PHYSICAL ORGANIC CHEMISTRY

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Reaction Rates, Equilibria, and Mechanisms

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PREFACE

It is one of the commonest occurrences in the development of science that the necessary subdivision of the subject leads to a temporary neglect of phenomena lying on the borders between the specialized fields. Sooner or later the deficiency becomes too patent to be overlooked, and a new specialty makes its appearance. Something of this sort has been happening in the last two decades on the borderline between physical chemistry and organic chemistry. For a time it was almost a point of honor with both physical and organic chemists to profess ignorance of the other's field, and it remains a useful defense mechanism, if any is needed, to excuse the fact that specialization entails limitation as well as intensification of knowledge. Meanwhile there has grown up a body of fact, generalization, and theory that may properly be called *physical organic chemistry*. The name implies the investigation of the phenomena of organic chemistry by quantitative and mathematical methods.

One of the chief directions that the development of the subject has taken has been the study by quantitative methods of the mechanism of reactions and of the related problem of the effect of structure and environment on reactivity. In no other direction have its results been of such immediate practical importance for the basic problem of chemistry, the control of chemical processes. This part of physical organic chemistry forms the subject of the present book.

A physicist colleague once mockingly referred to this kind of investigation as the study of soapmaking, whereas any respectable chemist must today busy himself with the chemistry of the nucleus. The remark underestimates both the theoretical and the practical significance of soapmaking. Soap is a by no means negligible factor in human civilization; I am not sure that we know more about the fundamentals of soapmaking, which is to say ester hydrolysis, than we do about the nucleus; I think the theoretical problems involved are quite as interesting; and I am convinced that an understanding of the mechanism by which

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complex naturally occurring substances, the enzymes, accelerate hydrolysis would lead to a great advance toward the interpretation of the phenomena of life.

Part of my excuse for this book is therefore that the material is important and interesting. In further justification I urge that the subject has reached a point of development where a unified and consistent treatment is possible in terms of a few simple generalizations and theories. My final apology is that no complete and adequate treatment is available except in widely scattered periodical articles. It is quite as difficult to advise a course of reading for a student of physical chemistry who wishes to assess the significance of an investigation of isotopic exchange phenomena in organic compounds as it is to aid a student of organic chemistry who wishes to understand the acid catalysis of the Beckmann rearrangement or of the cyclodehydration reaction. My hope is that this book may be of value to both groups, and I have therefore tried to make the discussion intelligible to a student with a sound but elementary knowledge of both physical and organic chemistry. I can only apologize if it contains matter that seems trivial or obvious to the advanced practitioner in either field.

The theories and principles presented in the text are to a very minor extent my own. For the mistakes I have no doubt made in crediting them to their true originators, I can only plead the great difficulty of determining the priority of ideas, and acknowledge my debt in general terms. I am indebted to the editor of the Journal of the American Chemical Society, to the publishers of Chemical Reviews, and to the Faraday Society for permission to reproduce a number of figures; to my colleagues at Columbia University for inspiration and advice, and especially to Prof. George E. Kimball, who has read and criticized part of the manuscript; to the research students who have taught me more than I have taught them; and most of all to three great teachers, E. P. Kohler, H. Staudinger, and J. M. Nelson, who planted the seed from which this book has grown.

<div align="right">Louis P. Hammett.</div>

Columbia University,
New York,
March, 1940.

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TABLE OF SYMBOLS AND OF VALUES OF CONSTANTS

A molar free energy—Helmholtz; any proportionality constant or variable parameter

$\unicode{x212B}$ ångstrom unit

a activity; any parameter

b any parameter

C molar heat capacity

c centigrade

c velocity of light *in vacuo;* 2.998×10^{10} cm./sec.

c concentration

d distance

d differential

∂ partial differential

E molar energy; potential difference

e electronic charge; 4.800×10^{-10} statcoulomb, 1.601×10^{-19} coulomb

e quantity of electricity

e base of natural logarithms

F Faraday's constant; 96,490 coulombs/mole

f partition function; activity coefficient

f function

G molar free energy—G. N. Lewis

g acceleration due to gravity; standard value, 980.6 cm./sec.^{2}

$g.$ gram

H molar heat content

h Planck's constant; 6.610×10^{-27} erg-sec.

h height

J mechanical equivalent of heat; 4.185 joules/cal.

K equilibrium constant

κ Kelvin

k Boltzmann's constant; 1.380×10^{-16} erg/deg.

k specific rate or rate constant

$l.$ liter

M molecular weight

м molar concentration

m rest mass of an electron; 9.104×10^{-28} g.

m mass in general; mass of an atom

$m.$ meter

N Avogadro's number; 6.026×10^{23} molecules/mole

N number of molecules

N normal concentration

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n number of moles
P pressure, probability factor in reaction-rate equation
p a priori probability
R gas constant per mole; 8.314×10^7 ergs/deg.-mole, 1.986 cal./deg.-mole.
      0.08206 l.-atm./deg.-mole
r radius
S molar entropy
s solubility
T temperature, absolute
t time
V volume
v rate of reaction (mole/l.-sec.); vibrational quantum number
W energy
Z number of molecular collisions per second
z valence of an ion
α degree of dissociation; angle of optical rotation
Δ increment
ϵ dielectric constant; energy per molecule
ϑ angle in polar coordinates
λ wave length
μ chemical potential (partial molal free energy of Lewis); ionic strength
ν frequency
Π product
π ratio of circumference to diameter
ρ reaction constant
Σ sum
σ diameter of molecule; substituent constant
ϕ potential energy of atomic system; angle in polar coordinates
Φ function
ψ wave function
$[\ ]$ enclosing the formula of a chemical substance, indicates its molar
         concentration

Ice point; 273.2κ
Gram-molecular volume; 22.414 l.

PHYSICAL ORGANIC CHEMISTRY

CHAPTER I

STRUCTURAL THEORY: NONELECTROLYTES

The Methods of Structural Chemistry.—The science of structural organic chemistry has developed from the study of chemical reactions pictures of the spatial arrangement of the atoms in organic compounds, which are astonishingly successful for the purpose for which they were designed—the qualitative prediction of the course of chemical reactions. The discovery of physical methods of investigation, which may be even more directly interpreted in terms of the geometry of the molecule, has led only to a verification and extension of the usefulness of these pictures. X-ray and electron-diffraction measurements, dipole-moment studies, investigations on surface films are all consistent with such ideas as the tetrahedral distribution of the valences of carbon, the hexagonal symmetry of benzene, the long-chain structure of stearic acid, and the accepted structures of the ortho, meta, and para derivatives of benzene and of the *cis* and *trans* isomers of ethylenic compounds.

As successful as these methods of structural determination have been, they nevertheless have their weaknesses and limitations, which have in fact long been apparent to the thoughtful organic chemist. The assumption of the constancy of valence has definitely failed to account for the properties of benzene derivatives, to say nothing of free radicals. The Walden inversion and the widespread occurrence of molecular rearrangements show that an entering group does not occupy the same position in space as the one that it displaces. Furthermore, although the organic chemist has developed to a fine art the prediction of the

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effect of structure and of external conditions upon course of reaction, reactivity, and yield of product, this is an art, as Conant once pointed out[1]; and it must be the task of science to replace the qualitative judgments with quantitative statements of reaction rate and reaction equilibrium.

Meanwhile the quantum theory of atomic and molecular structure has developed ideas that may be applied to these problems with illuminating and stimulating results. The basic concepts involved are presented in the following paragraphs; the reader who wishes a more detailed and exact mathematical treatment is referred to specialized treatises[2] and to the periodical literature.

Fundamental Ideas of Atomic and Molecular Structure.—In all current thought on the subject, the atoms and molecules of chemical substances are pictured as composed of nuclei and electrons. The nucleus is a positively charged body of extremely minute dimensions (with a diameter perhaps one one-hundred-thousandth of that of an atom). It is so dense that the mass of an atom is practically that of its nucleus. The charge of a hydrogen nucleus, a proton or a deuteron, is equal in magnitude but opposite in sign to the charge of the electron. More generally, the charge of a nucleus is equal to its atomic number multiplied by the charge of the hydrogen nucleus. Thus the nuclear charge of carbon is six, that of nitrogen seven, and that of oxygen eight times that of the proton. All electrons have the same negative charge and the same mass, approximately one eighteen-hundredth of that of the proton.

A neutral atom contains in addition to the nucleus a number of electrons electrically equivalent to the nuclear charge, *i.e.*, equal to the atomic number. An atom may, however, gain or lose electrons to become an ion of negative or positive charge. Thus the sodium atom contains 11 electrons, the sodium ion 10; the chlorine atom contains 17 electrons, the chloride ion 18. The earlier attempts to construct a theory of atomic and molecular structure in terms of nuclei and electrons pictured the latter as rotating about the nucleus in orbits like those of the planets about the sun. These theories have been abandoned in favor

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[1] CONANT, *Ind. Eng. Chem.*, **24**, 466 (1932).

[2] *E.g.*, PAULING and WILSON, "Introduction to Quantum Mechanics," New York, 1935; Hellmann, "Quantenchemie," Leipzig and Vienna, 1937.

of an approach, that of quantum mechanics, which is more difficult to visualize but much more useful.

The Quantum Principle: Energy Levels.—The chief source of information about the interior of the atom is the study in terms of the quantum principle of the absorption and emission of light by atoms and molecules. The quantum principle of Planck, Einstein, and Bohr amounts simply to this: When an atom or a molecule absorbs or emits light, it gains or loses an amount of energy, a quantum, the magnitude of which is equal to the fre-
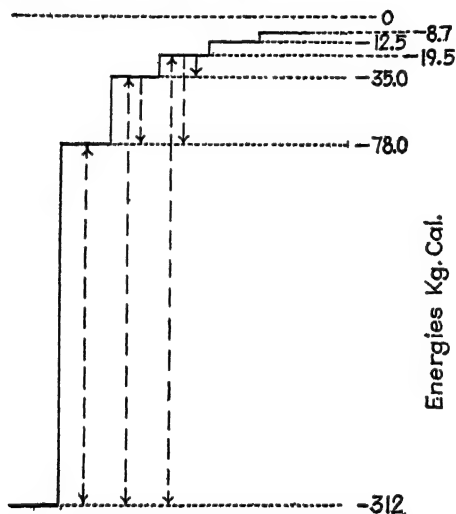
FIG. I-1.—Energy levels and transitions in the hydrogen atom.

quency of the light ν multiplied by a constant h which is called *Planck's constant* and has a value of 6.610×10^{-27} erg sec. If ΔE represents the change in energy per atom,

$$\Delta E = h\nu \qquad (1)$$

Since atoms and molecules absorb or emit only certain narrowly defined frequencies of light, *i.e.*, since they possess line spectra instead of continuous absorption or emission, equation (1) implies that their energies are correspondingly limited. An atom or a molecule can therefore have only certain sharply defined values of internal energy; it can exist in only one or

another of a series of energy states. Since each line in the spectrum corresponds to a transition from one energy state to another, the values of the energy that an atom or molecule possesses in its various states may be determined by investigating the frequencies of light that it can absorb or emit.

The possible energy values of the hydrogen atom, as revealed by its spectrum, may be represented, as in Fig. 1, by a series of steps of varying height. The energies of the states are given in kilogram-calories at the right of the diagram. Some of the possible changes in energy are represented by dashed arrows the length of which measures the energy change ΔE in kilogram-calories. By equation (1) the length of the arrow also measures the frequency of the light that is absorbed if the atom gains or that is emitted if it loses energy. There is a greater variety of emission than of absorption lines because almost all the atoms are normally in the lowest energy state, and only those transitions are possible which start from this state.

One may very naturally picture the increase in energy involved in going from a lower to a higher level as resulting from the removal of an electron to a greater distance from the nucleus, work being done against the attraction of the opposite charges of nucleus and electron. From the way in which the higher levels crowd together toward a limit, represented in Fig. 1 by the zero value of energy, it is reasonable to suppose that the limit represents the largest amount of energy that the atom can possess. The energy of the limit must then be that of a completely separated nucleus and electron, *i.e.*, of an ionized hydrogen atom, and the distance from lowest level to limit must measure the energy required for the ionization. This conclusion has been so completely and precisely verified in such a large number of experiments as to prove decisively the necessity of the quantum principle.

Quantum Mechanics: The Hydrogen Atom.—Evidence of this sort can obviously give no information about the position of the electron or about the rate at which it is moving; and it has indeed been impossible to find any mode of investigation that leads to such information. In accordance with this situation, the method of quantum mechanics concerns itself only with the probable or average position and motion of the electron.

The fundamental assumption of the quantum mechanics is expressed in a differential equation, the complexity of which increases with increasing number of nuclei and electrons, but which takes the form

$$\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial\psi}{\partial r}\right) + \frac{1}{r^2\sin^2\vartheta}\frac{\partial^2\psi}{\partial\phi^2} + \frac{1}{r^2\sin\vartheta}\frac{\partial}{\partial\vartheta}\left(\sin\vartheta\frac{\partial\psi}{\partial\vartheta}\right)$$
$$+ \frac{8\pi^2 mm}{h^2(m+m)}\left(W + \frac{e^2}{r}\right)\psi = 0 \quad (2)$$

in the simple case of the hydrogen atom (one nucleus of mass m and charge $+e$, one electron of mass m and charge $-e$). Here r is the distance from electron to nucleus, ϑ and ϕ are angles defining the position in space of the line joining nucleus and electron, W is the energy of the system, and ψ is the square root of the probability that an electron will be present at a point the polar coordinates of which are r, ϑ, and ϕ. This *Schrödinger* or *wave equation* cannot be proved or derived in the sense of inductive reasoning; it is a hypothesis or guess which is checked and found useful or valid by comparing with experiment the various conclusions that may be derived from it. And, in fact, all the known properties of hydrogen atoms and of other atomic and molecular systems agree in the minutest detail and to the utmost precision with the predictions of the equation.

Thus the equation has the peculiar property that it can be integrated to give a physically possible relation between the probability ψ^2 and the variables, r, ϑ, and ϕ only when the energy W has one or the other of a series of sharply defined values. These are given by the equation

$$W = -\frac{2\pi^2 mme^4}{(m+m)h^2n^2} = -\frac{W_H}{n^2} \quad (3)$$

in which n is any positive whole number and is called the *principal quantum number*. W_H has the value 311.934 kg.-cal./mole. But these values of energy are in fact just the ones, plotted in Fig. 1, that spectroscopic investigation has shown to be possible for the hydrogen atom. The prediction of the Schrödinger equation agrees therefore with the most striking property of atomic systems, the quantization of the energy.

Wave Functions or Orbitals.—For each value of n and consequently of W there exist one or more equations representing ψ as a function of r, ϑ, and ϕ. Some equations of this sort, called *wave functions* or *orbitals*, are

For $n = 1$

$$\psi = \frac{1}{\sqrt{\pi a_0^3}} e^{-r/a_0} \tag{4}$$

For $n = 2$

$$\psi = \frac{1}{4\sqrt{2\pi a_0^3}}\left(2 - \frac{r}{a_0}\right)e^{-r/2a_0} \tag{5}$$

$$\psi = \frac{1}{4\sqrt{2\pi a_0^5}} r e^{-r/2a_0} \cos\vartheta \tag{6}$$

$$\psi = \frac{1}{4\sqrt{2\pi a_0^5}} r e^{-r/2a_0} \sin\vartheta \cos\phi \tag{7}$$

$$\psi = \frac{1}{4\sqrt{2\pi a_0^5}} r e^{-r/2a_0} \sin\vartheta \sin\phi \tag{8}$$

The quantity a_0 in these equations is defined by

$$a_0 = \frac{h^2(m + m)}{4\pi^2 mme^2} = 0.5285\text{A} \tag{9}$$

The methods of integration by which equations of this sort are derived from the differential equation are devious and complicated. Fortunately there is no difficulty in determining whether the final result is correct; for it is a simple exercise in differential calculus to obtain the derivatives that appear in equation (2) from any of the equations (4) to (8) and by substitution of these and the correct value of W from equation (3) to verify the integration.

Each of the equations (4) to (8) represents a possible state of the hydrogen atom, *i.e.*, one of the ways in which the quantity ψ may vary from point to point in the space surrounding the nucleus. The transitions the energy and frequency of which are related by equation (1) are determined by changes of the atom from one to another of these states. For any value of n, there exist n^2 wave functions, all of which in the hydrogen atom have the same energy but which in any case represent different distributions in space. The angles ϑ and ϕ do not appear in one

of the wave functions for each value of n. In these states, which are called s states, the value of ψ depends only on the distance r of the electron from the nucleus and is independent of the direction in space of the line joining them. Equation (4) describes a $1s$ state, the only possible state for which $n = 1$, equation (5) a $2s$ state, and equations (6), (7), and (8) the three other states, called $2p$ states, which together with the $2s$ state make up the $2^2 = 4$ states for which $n = 2$. The letters d, f, and g are used to characterize other states, which are possible only when $n > 2$.
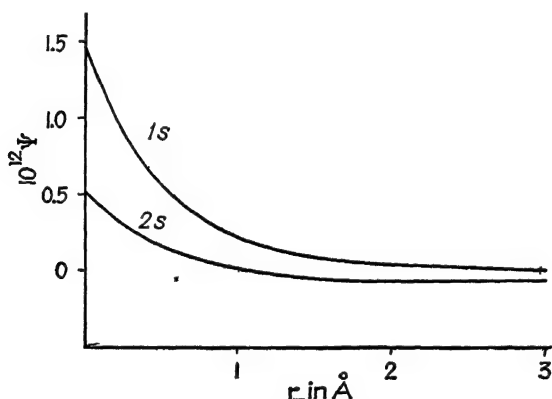
Fig. I-2.—The dependence of ψ on r in the $1s$ and $2s$ states of the hydrogen atom.

Various graphical representations are possible. Figure 2 plots the value of ψ against r for the $1s$ and $2s$ states of hydrogen. Another method is to plot on a plane through the nucleus lines connecting points of equal probability density ψ^2. Such contour maps are shown in Fig. 3 for the $1s$ state and in Fig. 4 for one of the $2p$ states. In these the value of ψ^2 along each contour differs by a constant amount from that along the next contour. This difference is indicated by the numerical values attached to the curves. The true contours are surfaces in three dimensions, which can be derived by rotating the curves plotted about a vertical axis through the nucleus.

The meaning of the probability density ψ^2 may be visualized by thinking of the electron as moving about very rapidly in the space surrounding the nucleus. Without attempting a detailed

description of this motion, one may then say that the probability
of the electron visiting a point is measured by the value of ψ^2
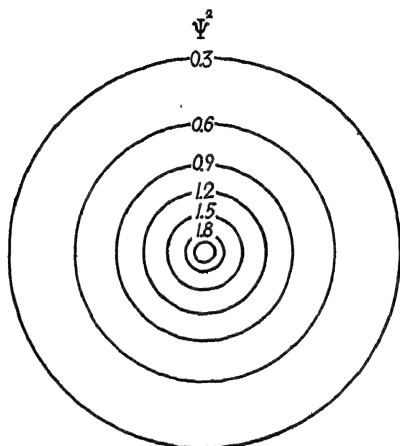
FIG. I-3.—ψ^2 contours for the 1s state of the hydrogen atom.
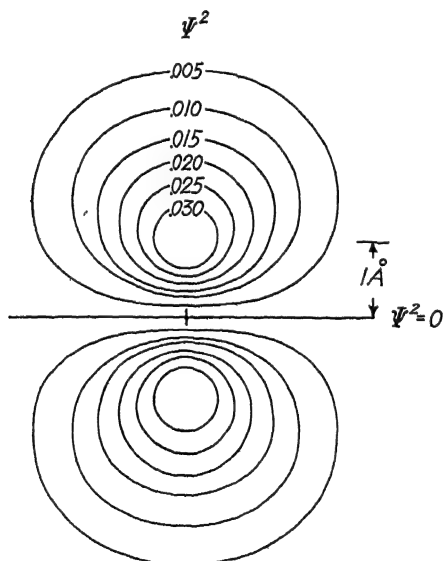
FIG. I-4.—ψ^2 contours for the 2p state of the hydrogen atom.

at that point. That is, the number of times the electron appears
at the point during any considerable period of time is propor-

tional to ψ^2. The effect of this situation would, in all essential respects, be the same as if the electron were diffused in space in such a way that the fraction of its charge present in a small volume of space dV in the neighborhood of a point is equal to the value of ψ^2 at the point multiplied by dV. Either picture is a possible and helpful one.

In all states the density drops off rapidly at large distances from the nucleus and becomes very small beyond a few Ångstrom units ($1A = 10^{-8}$ cm.). Nevertheless it never becomes equal to zero, which is approached only as a limit as r becomes infinite. In s states the density has its largest value in the immediate neighborhood of the nucleus and drops off symmetrically in all directions. In p states it is highest at two points on opposite sides of the nucleus and distant $1A$ or so from it; it is relatively high along the direction defined by these points and zero in a plane through the nucleus perpendicular to this direction. In p^- states, therefore, the electron, or rather its most probable position, has a well-defined direction in space.

Atomic Structures.—The mathematical difficulties encountered in integrating the Schrödinger equation increase rapidly when the number of particles involved exceeds the two, electron and nucleus, present in hydrogen. It has nevertheless been possible to account for the periodic system of the elements on the assumption that each electron in a many-electron atom can be assigned to a wave function or orbital of approximately the same sort as those described in equations (4) to (8) and that only two electrons can be assigned to any one orbital. These two are affected in opposite ways by a magnetic field and are said to have opposite spins because a spinning of the electron about an axis would lend it the property of reacting with a magnetic field. This limitation on the number of electrons permitted to an orbital is called the *Pauli exclusion principle*. In the case of the carbon atom, for example, it operates in the sense that there are two electrons in the $1s$ orbital, two in the $2s$, and two in two of the three possible $2p$ orbitals. The $1s$ electrons are so firmly bound and their average position is so close to the nucleus and so completely shielded by the less firmly bound $2s$ and $2p$ electrons that only the latter, which are called the *valence electrons*, are involved appreciably in the chemical reactions of the atom.

An atomic system in which all the orbitals of a particular kind are occupied has a marked stability, which is especially pronounced when the *s* and *p* orbitals of a given quantum number are completely filled. This property is exemplified both by the chemical inertness of the rare gases and by the great reactivity of the alkalies and the halogens. A helium atom possesses two electrons which just suffice to fill the 1*s* orbital. Because of the stability corresponding to this *filled shell*, the amount of energy required to remove one of the electrons is greater than that which can be furnished by attaching it to another atom, and the amount of energy that would be set free by adding a third electron in the 2*s* orbital is so small that it does not suffice to remove an electron from another atom. A similar inertness appears in neon, in which all 1*s*, 2*s*, and 2*p* orbitals are filled, and in the other rare gases. A sodium atom has one more electron than a neon atom, which must be in a 3*s* orbital, where it is only weakly held; a fluorine atom has one less electron than a neon atom, and the addition of an electron liberates considerable energy through the formation of the stable filled shell. Consequently, a sodium atom and a fluorine atom may react by transfer of an electron

$$Na + F \rightarrow Na^+ + F^- \tag{I}$$

with the evolution of a large amount of energy. Both the ions produced have the same stable electron configuration as neon. In the same way, the bivalence of magnesium may be attributed to the ease with which its two 3*s* electrons are lost to form Mg^{++}, which has the neon configuration, and that of sulfur to the stability of the argon configuration, which results when two electrons are added to form sulfide ion, $S^=$.

Electron Distributions in Molecules: The Hydrogen Molecule. It is known from the study of electrical discharges in hydrogen that a system of two hydrogen nuclei and one electron, the hydrogen molecule ion H_2^+, is stable in the sense that it does not fly apart, although it does have considerable tendency to capture an electron with the formation of neutral hydrogen, H_2. For this system an exact integration of the Schrödinger equation is still possible. The electron distribution that results is represented in Fig. 5 by a contour diagram on a plane through the two nuclei. The distribution in a plane perpendicular to the axis

joining the nuclei shows a high density at the axis, which drops off equally in all directions.   Because of this symmetry the state represented, which is the most stable state of the system, is analogous to the 1s state of a hydrogen atom.   Its most characteristic features are the concentration of the electron along the line joining the nuclei and the radial symmetry.

Calculation of the energy of this system and comparison with that of a hydrogen atom show that the process

$$H_2^+ \rightarrow H + H^+ \tag{II}$$

must require an energy of 60.84 kg.-cal., which is in close agreement with experiment.   Since the two nuclei would fly apart in the absence of the electron, it is proper to say that the electron
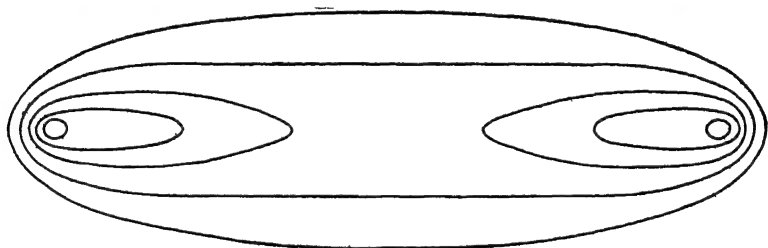
FIG. I-5.—ψ^2 contours for the hydrogen molecule ion, H_2^+, according to Burrau.

holds the nuclei together and that, being shared between them, it serves as a bond.

The neutral hydrogen molecule, with its two electrons, is a more difficult system with which to deal, and it has not been possible to construct a diagram of the kind shown in Fig. 5. The energy of the most stable state has, however, been calculated by a laborious process of successive approximations which leads to the result that the process

$$H_2 \rightarrow 2H \tag{III}$$

requires 102.69 kg.-cal., in excellent agreement with experiment. That is, two electrons, provided that they have opposite spins, can be shared between two nuclei in such a way as to produce a bonding which is materially stronger than that produced by one shared electron.   It is reasonable to suppose that the bonding electrons concentrate in the region between the nuclei, somewhat in the same fashion as the single electron of Fig. 5.

A most important property of this analysis is the conclusion that a hydrogen atom which is already combined with another hydrogen atom repels rather than attracts and combines with other atoms. This fact provides an explanation of and a mechanism for the phenomena referred to in the statement that the valence of hydrogen is 1. These phenomena are so familiar to the chemist that it is difficult for him to realize how serious a problem it has been to reconcile them with a physical picture of the atom. Ordinary physical forces do not exhibit the saturation characteristic of chemical valence. Thus a positively charged body like a sodium ion attracts negatively charged bodies like a chloride ion, but the mere fact that a sodium ion has already attracted one chloride ion does not prevent it from attracting others.

Fig. I-6.—The configuration of a hypothetical Na_2Cl_2 molecule.

If one slightly simplifies the situation by picturing the sodium and chloride ions as rigid spheres with the charges concentrated at the centers, the energy of formation of a sodium chloride molecule is given by

$$E_1 = -\frac{e^2}{r} \qquad (10)$$

with r the distance between centers of the ions. If two such molecules are brought together to form the structure shown in Fig. 6, the energy of the resulting system is found, by summing the interactions of the individual ions, to be

$$E_2 = -4\frac{e^2}{r} + 2\frac{e^2}{\sqrt{2}r} = -2.59\frac{e^2}{r} \qquad (11)$$

Consequently, the combination of two sodium chloride molecules to form the polymer sets free an amount of energy which is 59 per cent as large as that liberated in the combination of one sodium ion and one chloride ion to form a molecule of NaCl. Because of the simplification of the model, the result is only

approximate, but there can be no doubt of the qualitative conclusion that two sodium chloride molecules must cling together. A continuation of this calculation accounts for the stability of crystalline sodium chloride in which each sodium ion has as equidistant nearest neighbors not merely two but six chloride ions.

Two hydrogen molecules, on the other hand, attract each other only by virtue of the very weak forces, generally called van der Waals' forces, which act between all molecules and atoms, even those of the inert gases. A rough measure of the difference in strength between the van der Waals' forces and the valence forces may be derived from a comparison of the temperature, $20.4°\text{K}$, required to separate the molecules of hydrogen from each other by boiling the liquid with that necessary to produce appreciable dissociation of the molecule into atoms, which is about $2000°\text{K}$.

More Complicated Molecules : The Lewis Valence Theory.— It has not been possible to determine the energies, much less the electron distributions, of more complicated structures than H_2 by the way of exact and rigid mathematical reasoning from the Schrödinger equation. Nevertheless it has been shown by Heitler, London, Slater, and Pauling that it is at least consistent with the requirements of the equation to suppose that all valence links in saturated chemical compounds are of much the same nature as that between the two hydrogen atoms in H_2. This hypothesis goes far to explain and correlate chemical valence theory or, more exactly, to justify theoretically and lend definiteness and precision to a set of rules formulated by G. N. Lewis in 1916. Lewis observed empirically that almost all the facts of chemical valence can be interpreted if one supposes that each valence link is formed by a pair of electrons shared between the linked atoms and that in nearly all stable molecules the total number of valence electrons, whether shared or unshared, assignable to each atom has a definite value characteristic of the element. This is 2 for hydrogen, 8 for the lighter elements up to chlorine, and 8, 12, or 16 for the heavier ones. For the lighter elements these numbers are identical with the number of electrons in the outer shell of the next heavier inert gas; consequently, one may state Lewis' rule in the following form: The

atoms of the lighter elements tend strongly to attain a rare-gas configuration, by loss, by gain, or by sharing of electrons.

In the quantum mechanical interpretation the bond is due to two electrons of opposite spin, which are concentrated symmetrically about the line joining the nuclei of the atoms that they bond. They are not however definitely fixed in position, the axis of the link being merely the most probable position. A carbon atom with its four valence electrons may form electron-pair bonds with four hydrogen atoms, each of which contributes one electron. The electrons in each pair lie, to a large extent, in the neighborhood of the line joining the carbon atom to the particular hydrogen atom that they bond. The total eight electrons satisfy the tendency of carbon to hold eight valence electrons and, simultaneously, that of each hydrogen to hold two. Any further electrons must therefore be very weakly bound. Consequently, methane has no measurable tendency to share electrons with other atoms and molecules and is a highly saturated substance. The formula may be written

$$\begin{array}{ccc} & H & & H \\ & \overset{..}{} & & | \\ H:&\!\!C\!\!&:H & \quad or \quad H-\!\!\overset{|}{C}\!\!-H \\ & \overset{..}{} & & | \\ & H & & H \\ & & (A) & \end{array}$$
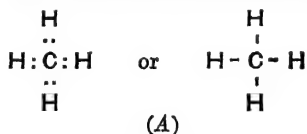
In the first case each dot represents a valence electron, in the second each dash represents a valence bond and is to be understood as symbolizing a pair of shared electrons; in both cases the symbol represents a concentration, not a fixation, of the electrons.

A nitrogen atom carries five valence electrons. When it has reacted with three hydrogen atoms, each with one electron, the total number of valence electrons reaches eight: then the nitrogen atom has attained its full quota of electrons and can react with no more hydrogen atoms. Of the eight electrons, six are shared with hydrogen atoms; the other two, which are sometimes called a *lone pair*, are unshared. The formula is

$$\begin{array}{ccc} & H & & H \\ & \overset{..}{} & & | \\ H:&\!\!N\!\!&: & \quad or \quad H-\!\!\overset{|}{N}\!\!\,\cdot \\ & \overset{..}{} & & | \\ & H & & H \\ & & (B) & \end{array}$$
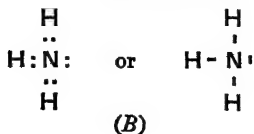
The first symbol is obvious; in the second each dash still represents a pair of electrons, shared or unshared (page 25). Although ammonia is saturated with respect to hydrogen atoms, it is not with respect to hydrogen ions, which are bare protons. Attachment of a proton to the unshared pair leads to the completely saturated ammonium ion (C)

$$\left[\begin{array}{c} H \\ | \\ H-N-H \\ | \\ H \end{array}\right]^+ \qquad \begin{array}{c} H \\ | \\ {}^{\cdot}O-H \\ {}_{-} \end{array} \qquad \left[\begin{array}{c} H \\ | \\ H-O-H \\ {}_{-} \end{array}\right]^+$$

$$(C) \qquad\qquad (D) \qquad\quad (E)$$
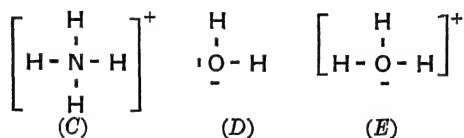
Similar consideration applied to oxygen leads to the structures (D) and (E) for water and oxonium ion, respectively. In principle an ion OH_4^{++} should be possible, but its formation would require an extraordinarily high and, in fact, unattainable acidity. In the presence of water, for instance, the reaction

$$OH_4^{++} + H_2O \rightarrow 2OH_3^+ \tag{IV}$$
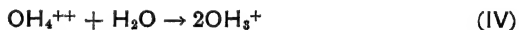
would go practically to completion.

Some more or less empirical properties of the valence link may be added to the picture. The direction in space of the four electron pairs, or rather of their most probable positions, is that of the vertices of a tetrahedron. The tetrahedral arrangement of the carbon valences and of the four nitrogen valences in derivatives of ammonium ion is familiar from stereochemical grounds; it has been confirmed by a wide variety of physical methods. That approximately the same arrangement persists when some of the electron pairs are unshared appears from the thoroughly demonstrated dissymmetry of ammonia and water. Dipole moment, specific heat, and absorption spectrum unite in demonstrating that the oxygen nucleus does not lie on the line joining the two hydrogen nuclei. Similar evidence indicates that the three hydrogen nuclei in ammonia form an equilateral triangle with the nitrogen atom lying perpendicularly above the center of the triangle and definitely out of its plane. These are the configurations to be expected if two or three of the vertices of the tetrahedron carry hydrogen atoms and the others lone pairs.

Because the electronic distribution is radially symmetrical about the axis of the bond (page 11), no disturbance results and no expenditure of work is necessary when one atom is rotated with respect to the other. Thus in ethane one CH_3 group may be rotated about the C—C link so easily that isomers differing in the relative orientation of the groups do not exist. The picture permits, therefore, the free rotation about the saturated bond which is required by the chemical facts. The rotation is however not entirely free, probably because of repulsions between the hydrogen atoms, and this leads to effects observable in the behavior of the specific heats at low temperatures.[3]

Unsaturated Compounds: The Hückel Treatment.—With unsaturated compounds the chemical facts themselves do not permit the assumption of definite, indivisible, and saturable valences. The failure of these concepts is indicated by the necessity of introducing such ideas as the partial valence of Thiele. The formula $CH_2{=}CH{-}CH{=}CH_2$ is an unsatisfactory one for butadiene with its capacity for 1,4 addition, and no satisfactory valence-bond picture has ever been written for benzene. Naturally the quantum mechanical picture of the saturated valence leads to no advance.

One possible attack[4] starts from an approximate quantum mechanical demonstration that a carbon atom attached to three instead of the usual four atoms, and carrying therefore a single unshared or odd electron, is in its most stable state when it lies at the center of a triangle formed by the three atoms to which it is linked and in the same plane with them. Because of the odd electron the structure is strongly unsaturated although stable. This corresponds to the known properties of the methyl radical which does not break down into smaller fragments but does have a large tendency to associate to valence-saturated compounds like ethane. The probability density of the odd electron has a maximum value along a line perpendicular to the plane of the atoms and is zero in the plane; in fact it is much like that for the hydrogen $2p$ electron shown in Fig. 4. Electrons of this

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[3] KISTIAKOWSKI, LACHER, and STILL, *J. Chem. Phys.*, **6**, 407 (1938).

[4] E. Hückel has given an excellent review of these ideas, which are largely due to his work, *Z. Elektrochem.*, **43**, 752; 827 (1937).

kind may very suitably be called *unsaturation electrons*;[5] they have also been called *electrons of the second kind*.[4]

When two atoms each carrying an unsaturation electron are linked together by an ordinary electron-pair bond, the two unsaturation electrons interact in such a way as to still further stabilize the structure. They may therefore be said to form a second shared pair, which helps to bind the atoms together; but the binding is less firm than that due to the ordinary bond,
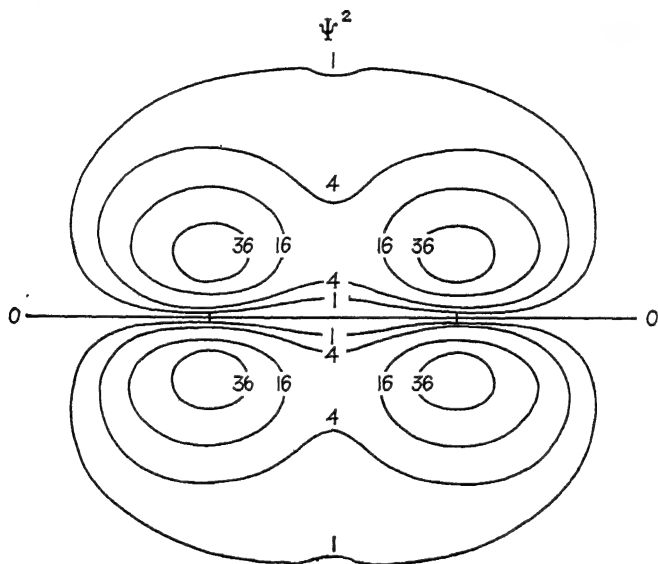
FIG. I-7.—ψ^2 contours of the unsaturation electrons in ethylene.[4]

and the nature of the electronic distribution is very different. Electron density contours for the unsaturation electrons in ethylene, the type compound of this sort, are shown in Fig. 7. The plane of the diagram is perpendicular to the one that contains the hydrogen and carbon nuclei. Instead of being concentrated between the nuclei that they link, these unsaturation electrons lie chiefly above and below the plane of the molecule and have a zero density in that plane.

This picture is in excellent agreement with the properties of olefinic compounds. The best estimate, none too reliable it must

[5] MULLIKEN, *J. Chem. Phys.*, **7**, 339 (1939).

be admitted,[6] of the work required to rupture a carbon-carbon single bond is 84.1 kg.-cal. and of that required to rupture the double bond 151.2. The difference, 67.1 kg.-cal., may be taken approximately as the binding energy due to the unsaturation electrons. The increased firmness of binding is even more directly evidenced by the internuclear distances. Two carbon atoms joined by a single bond show a distance between nuclei of 1.54A. The corresponding distance in ethylene is 1.34A. Because of the concentration of the unsaturation electrons in the region above and below the plane of the nuclei, rotation of one CH_2 group about the line joining the two carbon atoms sets up a new, less stable electron distribution and requires the expenditure of considerable work. This fact accounts for the existence of *cis* and *trans* isomers. The characteristic chemical unsaturation of olefins may be attributed to the way in which the unsaturation electrons spread out in space, ready to capture other atoms; the high refractivity may be accounted for by the weaker binding of these electrons, which are more easily displaced in the electromagnetic field of a light wave; and the absorption of light in the ultraviolet (page 60) to much the same reason.

The most important property of substances containing unsaturation electrons is the lack of definite integral valences. When three or four or more carbon atoms carrying electrons of this kind are linked in a chain, they do not interact in the way suggested by the formula $CH_2{=}CH{-}CH{=}CH_2$. Rather the unsaturation electrons on each carbon interact with those on its neighbors in the way suggested by the formula $CH_2{=}CH{=}CH{=}CH_2$.

One of the methods[4] which has been used to approach the theory of such a system, called the *method of molecular orbitals,* abandons entirely the attempt to localize the unsaturation electrons in particular valence links. Instead, it considers how these electrons may be added to a structure composed of the nuclei and the electrons that form the saturated bonds in the same way that the theory of many-electron atoms approaches the problem of adding electrons to a single nucleus. It then appears that there is a series of molecular orbitals of increasing energy into each of which two electrons of opposite spin may be

[6] PAULING and SHERMAN, *J. Chem. Phys.*, **1**, 606 (1933). KISTIAKOWSKI, *J. Phys. Chem.*, **41**, 175 (1937).

put.   These are analogous to the $1s$, $2s$, $2p$, etc., orbitals of the atomic problem.   In both cases certain preferred numbers of electrons, which just suffice to fill all the orbitals of a given kind, confer an especial stability on the system.   The relative unreactivity of conjugated double-bond systems, and especially that of aromatic compounds, comes out of this treatment as a phenomenon closely related to the inertness of the rare gases.   In general, any even number of unsaturation electrons yields a more stable system than the adjacent odd ones, chiefly because two electrons of opposite spin suffice to fill each orbital.   In this way, one accounts for the fact that butadiene with four unsaturation electrons is less prone to polymerization than the allyl radical which has three.

The detailed analysis by this method indicates that the four unsaturation electrons in butadiene are spread out over all four carbon atoms and occupy two of the orbitals of the molecule. The two electrons in the orbital of lowest energy act to hold all the carbons together and to resist rotation about any of the linkages; the other two link the end pairs but weaken the linkage of the middle pair.   The net effect is a molecule in which all the carbons are bound by linkages that are intermediate in strength between single and double bonds and that possess the property of resisting rotation.   It is to be expected that the linkage between the two middle carbon atoms should be weaker than the end linkages, the distance between the atoms should be greater, and the resistance to rotation weaker.

In benzene there are six unsaturation electrons, and the carbon and hydrogen atoms lie in a plane with all valence angles equal to 120 deg.   The quantum mechanical treatment shows that, in ring systems in a plane, a group of six electrons makes up a filled shell of great stability, thus accounting for the relative saturation of benzene.   In cyclobutadiene and cyclooctatetraene there are too few or too many electrons to yield this filled-shell stability.   In addition, these rings can be built up only by a considerable distortion either of the normal 120-deg. valence angle or of the planar configuration, both of which are required in atoms bound by unsaturation electrons.

The Pauling Treatment: Resonance.—Another method of attack on the problem of unsaturated and aromatic compounds

makes use of a concept that is called *resonance* in quantum mechanical theory. The concept appears even in so simple a case as that of H_2^+ when the attempt is made to obtain an expression of the wave function by a method of successive approximations. If one represents the two hydrogen nuclei by H_a^+ and H_b^+, respectively, a reasonable first approximation might be to suppose that H_2^+ behaves like an assembly of nucleus H_a^+ with atom H_b and to consider how the known wave function of the latter is affected by the proximity of the former. But one could equally well start with the assumption that it behaves like an assembly of nucleus H_b^+ with atom H_a. If the wave functions based upon these two assumptions be ψ_a and ψ_b, respectively, then some combination $x\psi_a + y\psi_b$ must be a better approximation to the real wave function than either ψ_a or ψ_b alone, and one can proceed to the determination of the values of x and y which best fit the Schrödinger equation. This approach has led to excellent results in many problems of atomic and molecular structure. When this method can be applied, the system is said to *resonate* between the structures represented by $H_a^+ + H_b$ and by $H_b^+ + H_a$, and the actual state of the system is said to be a *resonance hybrid* of these structures.

By generalizing this result it may be shown that, whenever two or more structures of not too different energy may be taken as first approximations to the true electronic distribution, the actual wave function may to a considerably better approximation be represented as a superposition, a linear combination, of the wave functions representing those structures. The system is then said to resonate between the structures and to be a resonance hybrid of them.

The detailed mathematical analysis brings out the perhaps unexpected but certainly not unreasonable result that the actual energy of the system is less than that of any of the resonating structures. Consequently, the actual system shows a greater stability and a lower reactivity than would be expected from any of the resonating structures. ☛ The difference in energy between the actual system and that predicted for one of the resonating structures is called the *resonance energy*. It is largest and the resulting stabilization most effective when the resonating structures are of equal energy. When one of the structures is of mate-

rially lower energy than the others, the actual state approaches closely to that represented by the structure of lowest energy, and the resonance hybrid is said to contain only a minor contribution from the structures of higher energy. In general, the properties of the actual state, other than the energy, will resemble each of the resonating structures in proportion to the contribution that it makes to the actual wave function.

There is an important limitation on the resonating structures in that they must be independent. This means that it must not be possible to derive one of them by superposition of the others.

TABLE I.—HEATS OF HYDROGENATION AND OF BROMINATION IN THE GAS STATE AT 82°C

ΔH in kilogram-calories for the addition of one mole of hydrogen or bromine[7]

Substance	H$_2$	Br$_2$	Substance	H$_2$
Ethylene................	−32.8	−29.058	2,3-Dimethylbuta-	
Propylene..............	−30.1	−29.412	diene..............	−27.3
1-Butene...............	−30.3	−29.585	Cyclohexadiene......	−26.8
1-Heptene..............	−30.1		Cyclopentadiene.....	−24.0
t-Butylethylene..........	−30.3		Phenylethylene......	−28.6
as-Dimethylethylene......	−28.4		Benzene.............	+ 5.6
s-Dimethylethylene, *trans*.	−27.6	−29.075	Ethylbenzene........	+ 6.5
s-Dimethylethylene, *cis*...	−28.6	−30.177	Mesitylene..........	+ 5.9
Trimethylethylene.......	−26.9	−30.398	*o*-Xylene............	+ 8.1
Tetramethylethylene.....	−26.6		Vinyl acetate........	−31.1
Cyclopentene............	−26.9		Crotonaldehyde......	−25.2
Cyclohexene.............	−28.6		2-Ethoxypropene.....	−25.1
Allene..................	−41.2		Acetone.............	−13.4
Butadiene...............	−29.5		Methylethylketone...	−13.2
			Allyl alcohol........	−31.5
			Ethyl vinyl ether.....	−26.7
			Acetaldehyde........	−16.75

By the resonance approximation, butadiene is a hybrid of the structures $CH_2=CH-CH=CH_2$ and $\cdot CH_2-CH=CH-CH_2\cdot$, the dots representing unpaired electrons. Since the second

[7] CONANT and KISTIAKOWSKI, *Chem. Rev.*, **20**, 181 (1937). CONN, KISTIAKOWSKI, and SMITH, *J. Am. Chem. Soc.*, **60**, 2764 (1938). DOLLIVER, GRESHAM, KISTIAKOWSKI, SMITH, and VAUGHAN, *ibid.*, **60**, 440 (1938).

structure with its odd electrons has a higher energy than the first, the actual state resembles the first structure more than the latter. Consequently, the middle linkage should have less double-bond character in terms of interatomic distance and freedom of rotation than the end ones. Because of the resonance energy, greater amounts of energy of reaction or of activation should be necessary in the case of butadiene than in that of ethylene, *i.e.*, the diene should be less unsaturated. These conclusions are identical with those obtained by the method of molecular orbitals and are consistent with the properties of the substance.

Benzene is a hybrid of the two Kekulé structures (*F*) and (*G*) in equal amounts, together with a considerably smaller contribution from the three Dewar structures (*H*), (*I*), and (*J*)
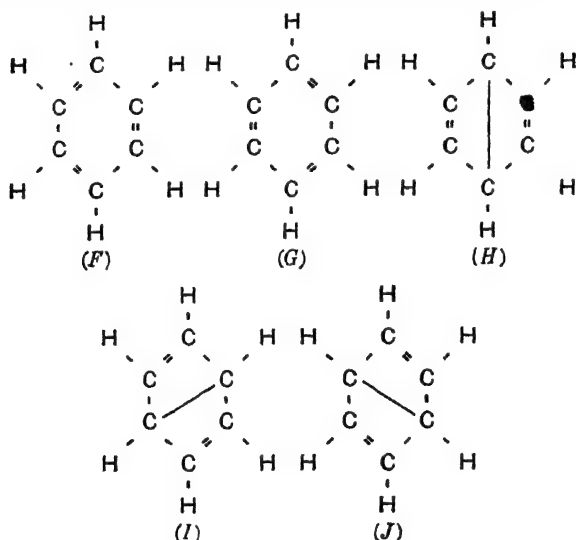
Its relative saturation is accounted for by the large resonance energy that appears when two structures are of equal energy.

Resonance and Heats of Addition Reactions.—Since the addition of hydrogen, bromine, or the like destroys the resonance in a system of conjugated double bonds, the reaction can occur only if the resonance energy is supplied. Although a heat of reaction must be used with caution as a measure of resonance energy,

which is a potential energy quantity (page 77), the effect is so large in the case of benzene derivatives as to be unmistakable. As the data in Table I show, the amount of heat liberated in the addition of one mole of hydrogen to a hydrocarbon with a single double bond varies from 32.8 to 26.6 kg.-cal., whereas the addition of one mole of hydrogen to a benzene hydrocarbon requires the absorption of 6 to 8 kg.-cal. The resonance energy of benzene is actually greater than the quantity of energy set free by the addition of hydrogen to the double bond so that the sign of the heat of reaction reverses.

In the case of butadiene the resonance energy is so small that it is masked by structural factors.

Resonance and Interatomic Distances.—When, as a result of resonance, linkages are intermediate in character between single and double bonds, the length of the link is also intermediate. The internuclear distances involved have been determined in a variety of ways, notably from X-ray diffraction in crystals, from X-ray and electron diffraction in gases, and from infrared, Raman, and band spectra.[8] The results of the different methods are consistent and show that the length of a particular kind of linkage is very constant. Within the experimental error of 0.03A the length of a carbon-carbon single bond has the constant value of 1.54A in diamond, ethane, propane, *i*-butane, neopentane, cyclopentane, cyclohexane, *i*-butene, tetramethylethylene, mesitylene, and hexamethylbenzene. The length of the double bond is 1.34A in ethylene and allene; that of a triple bond 1.20A in acetylene. The hybrid bonds in benzene have the intermediate length of 1.39A, in naphthalene and anthracene 1.41A. In graphite, which consists of layers of a practically infinite number of condensed benzene rings [structure (*K*)] with weak van der Waals' binding between layers and which is the limiting case of an infinitely extended polynuclear aromatic hydrocarbon, the carbon-carbon distance is 1.42A. In cyclopentadiene (*L*) the bond marked with a star has a length of 1.46A, showing as predicted (page 21) a relatively large proportion of single-bond

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[8] (*a*) Earlier data are given in Stuart, "Molekülstruktur," Berlin, 1934; (*b*) later electron diffraction measurements, by Pauling, Brockway, and Beach, *J. Am. Chem. Soc.*, **57**, 2705 (1935); Pauling and Brockway, *ibid.*, **59**, 1223 (1937). The theory is due to Pauling *et al.*

(K)   (L)
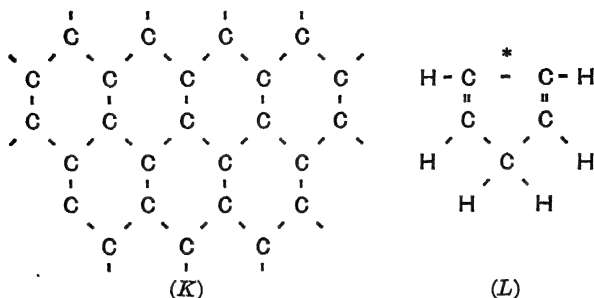
character.   Similarly, the link between the two rings in biphenyl has a length of 1.48A and the central link in $N\equiv C\!-\!C\equiv N$ and in $HC\equiv C\!-\!C\equiv CH$ one of 1.43A.   The carbon-carbon link in carbon suboxide (M)

(M)
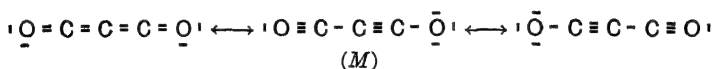
which resonates between doubly and triply bonded structures shows an appropriate length, 1.30A.
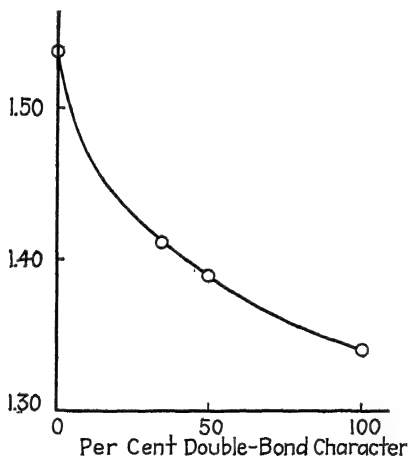
Fig. I-8.—Interatomic distance and double-bond character.[85]

The bonds in benzene may be said[85] to have one-half double-bond character, since the principal resonating structures are the two Kekulé ones (F) and (G).   Any carbon-carbon bond is a single bond in one of these and a double bond in the other, and

the two structures contribute equally to the actual state of the system.   In graphite each bond has, by the same reasoning, one-third double-bond character.   A plot of carbon-carbon distance against fraction of double-bond character may therefore be set up as in Fig. 8.   The scantier data available for carbon-oxygen, carbon-nitrogen, and nitrogen-oxygen bonds fit curves of similar shape.

· From interpolation on these curves one may then estimate the fraction of double-bond character in unknown cases from the measured interatomic distances.   Thus the bond previously referred to in cyclopentadiene has 20 per cent double-bond character, as does the internuclear bond in biphenyl.   The carbon-nitrogen bond in urea is thus estimated[85] to have 28 per cent double-bond character.   This value is not far from the 33 per cent that it would have if the three structures (N), (O),

$$\bar{N}H_2 \qquad\qquad NH_2 \qquad\qquad \bar{N}H_2$$
$$|O=C \qquad\qquad |\bar{O}-C \qquad\qquad |\bar{O}-C$$
$$NH_2 \qquad\qquad NH_2 \qquad\qquad NH_2$$
$$(N) \qquad\qquad\quad (O) \qquad\qquad\quad (P)$$
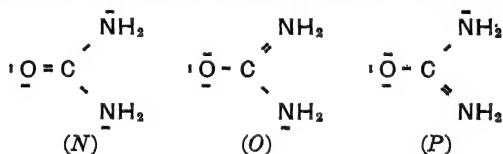
and (P) were equally important.

A more complete theoretical treatment[9] leads to a quantity called the *order* of a bond.   This order is 1 for a single bond, 2 for a double bond, 3 for a triple bond, 1.623 for benzene, and 1.45 for graphite.

Symbols.—Although no symbolism can completely represent the finer details of these ideas of structure and valence, some alterations in the classical structural formulas are well worth while.   Since each valence bond depends upon a pair of electrons, it is unnecessary[10] to replace the dash, which is the traditional symbol for the bond, by another representation, such as two dots for the two shared electrons; all that is necessary is to understand that the dash means a pair of electrons.   For an unshared pair one avoids confusion with the old symbol for a free valence by writing the dash parallel, rather than perpendicular, to the symbol of the atom.   Formulas (A) to (E) are of this

[9] PENNEY, *Proc. Roy. Soc.* (London), **A158**, 306 (1937).
[10] EISTERT, *Ber.*, **71B**, 237 (1938).

type as are the following structures for methanol (Q), methyl amine (R), and methyl iodide (S):
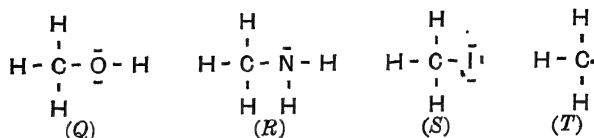
An odd or unpaired electron may be represented by a dot, which gives the methyl radical the symbol (T).

An unconjugated double bond may be represented by its classical formula without attempting to indicate the difference in the nature of the two links making up the double bond. Two alternative methods may be used with a conjugated system. In the light of the Hückel treatment, dotted lines may be drawn to indicate the interaction of the unsaturation electrons as in the symbols (U) and (V). Or one may write the symbols for the resonating structures with a double-pointed arrow between
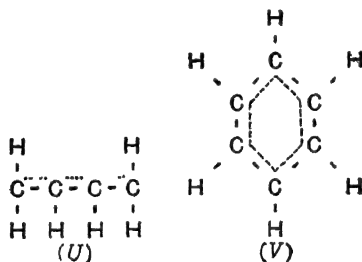
them[11] as in (W).
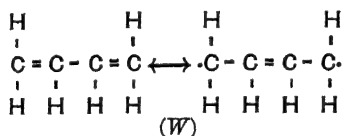
Abbreviations of an obvious sort are almost inevitable, *e.g.*, H_3C—$\bar{O}$—H for methanol, $H_3C\cdot$ for the methyl radical.

Contrast between Resonance and Tautomerism.—The resonance idea must not be confused with that of tautomerism. The

[11] BURY, *J. Am. Chem. Soc.*, **57**, 2115 (1935). EISTERT, *Angew. Chem.*, **49**, 33 (1936).

resonance picture does not at all imply that benzene oscillates or tautomerizes between the two Kekulé structures with the bonds slapping back and forth like some mechanical apparatus. One can in no sense account for the stability and relative unsaturation of benzene by supposing that it is a mixture in mobile equilibrium of the forms represented by the resonating structures. The mixture, like its components, must show the characteristic properties of olefinic substances. The essential feature of the resonance idea is that of a state intermediate between those represented by the resonating structures, a state to the properties of which one can make a useful first approximation by combining the properties of the latter, but which possesses in addition its own distinctive properties, notably the resonance energy that stabilizes and decreases the reactivity of the system. The idea of an intermediate state, called a *Zwischenzustand*[12] or the *mesomeric state*,[13] had appeared in organic chemical theory before the quantum mechanical resonance method was applied; it is only through Pauling's application of this method that the stability, which is the most striking property of resonating systems, has been accounted for.

Restricted Rotation in Bonds of Mixed Type.—A notable verification of the predicted properties of resonating systems has appeared[14] in connection with the infrared light absorption of phenols. These have a characteristic absorption[15] in a region of wave length in which for various reasons it is believed that the absorption depends upon vibrations of the phenolic hydrogen to and from the oxygen to which it is linked. Phenol shows one absorption band at 7050 cm.$^{-1}$, 2,4,6-trichlorphenol one at 6890, but o-chlorphenol absorbs at two frequencies, 7050 and 6910. These phenomena may be interpreted as follows:[14] In addition to the various structures of the benzene ring, a resonance is possible in phenol which involves the unshared electrons on the oxygen atom. Some of the structures involved are shown in (X) to (Z). (X) is the classical formula; (Y) may be constructed from it by the formation of a double bond between the

[12] ARNDT and EISTERT, *Z. physik. Chem.*, **B31**, 125 (1936).

[13] INGOLD, *Chem. Rev.*, **15**, 225 (1934).

[14] PAULING, *J. Am. Chem. Soc.*, **58**, 94 (1936).

[15] WULF and LIDDEL, *J. Am. Chem. Soc.*, **57**, 1464 (1935).

$$(X) \qquad\qquad (Y) \qquad\qquad (Z)$$
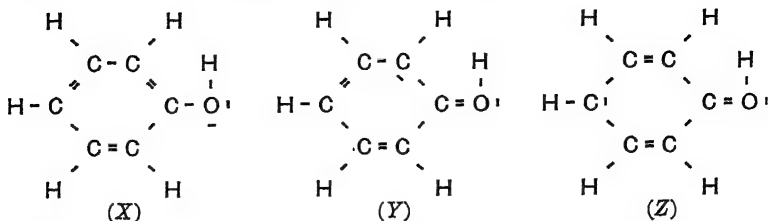
oxygen and its adjacent ring carbon. This uses an unshared pair on the oxygen and, consequently, sets free as an unshared pair on the ortho carbon atom the unsaturation electrons previously involved in forming the double bond in the ortho position. A similar operation on the other Kekulé structure puts the unshared pair on the other ortho carbon; a repetition of the process puts it on the para carbon as in (Z). There is, however, no way by which the unshared pair may reach the meta carbons.

There is therefore a significant proportion of double-bond character in the carbon-oxygen link, and this restricts the freedom of rotation and tends to hold the phenolic hydrogen in the plane of the ring. Since two groups attached to oxygen do not lie in a straight line (pages 15, 33), it may be directed up as shown in (X) to (Z) or down. This makes no difference in phenol or in trichlorphenol, since the two directions are identical; the lower frequency in the latter case indicates that proximity to chlorine slows down the vibrations of the hydrogen. In *o*-chlorphenol, however, two kinds of molecule are possible, one with the phenolic hydrogen pointing toward chlorine, the other with the hydrogen pointing toward the other side of the ring. The former might be expected to absorb at the same frequency as trichlorphenol, the latter at that of phenol. The frequencies of the double absorption of *o*-chlorphenol correspond closely to this prediction. The same effects have been observed in a number of other phenol derivatives.[16]

Resonance and the Reactivity of Halogen.—In vinyl chloride the unshared electrons on the halogen permit a resonance by virtue of which the carbon-chlorine linkage attains a certain proportion of double-bond character and the chlorine becomes more firmly bound than when it is attached to saturated carbon.[8b]

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[16] WULF, LIDDEL, and HENDRICKS, *J. Am. Chem. Soc.*, **58**, 2287 (1936).

$$
\begin{array}{ccc}
\text{H} & \text{H} & \text{H}\\
\diagdown & \diagup & \\
\text{C} = \text{C} & \longleftrightarrow & \text{H} - \overset{\cdot\cdot}{\text{C}} - \text{C}\\
\diagup & \diagdown & \\
\text{H} & \overset{\cdot\cdot}{\underset{\cdot\cdot}{\text{Cl}}} & \text{H} \qquad \overset{\cdot\cdot}{\underset{\cdot\cdot}{\text{Cl}}}
\end{array}
$$

(*AA*)
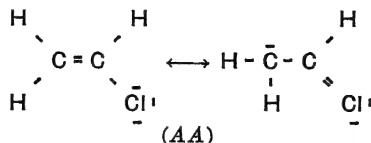
The existence of this effect is clearly demonstrated by the shortened bond lengths shown in Table II. The theory is further supported by the fact that the shortening is less apparent and the percentage of double-bond character smaller in those chlorinated ethylenes which contain the largest numbers of chlorines.

TABLE II.—INTERATOMIC DISTANCES AND BOND TYPES OF CARBON-CHLORINE BONDS[8b,17,18]

Molecule	C—Cl distance, A	% double bond	Molecule	C—Cl distance, A	% double bond
CCl_4	1.74	0	$COCl_2$	1.68	17
$CHCl_3$	1.77	0	$CSCl_2$	1.70	12
CH_2Cl_2	1.77	0	C_6Cl_6	1.70	12
$CH_2{=}CHCl$	1.69	14	C_6H_5Cl	1.69	
$CH_2{=}CCl_2$	1.69	14	$p\text{-}C_6H_4Cl_2$	1.69	
$CHCl{=}CHCl$ *cis*	1.67	20	$m\text{-}C_6H_4Cl_2$	1.69	
$CHCl{=}CHCl$ *trans*	1.69	14	$1,3,5\text{-}C_6H_3Cl_3$	1.69	
$CHCl{=}CCl_2$	1.71	10	$o\text{-}C_6H_4Cl_2$	1.71	
C_2Cl_4	1.73	6	$1,2,4,5\text{-}C_6H_2Cl_4$	1.72	

Each additional halogen introduces a new possibility of resonance and decreases thereby the proportion of any given structure in the combination; thus in tetrachlorethylene there are five structures, and any given chlorine is double bonded in only one of them. The examples of phosgene and thiophosgene show that the same bond shortening appears when halogen is linked to a carbon that is doubly linked to oxygen or bound to sulfur.

Triphenylmethyl.—The problem of the stability of triphenylmethyl has been attacked with notable success by similar methods.[4,19,20] The classical structure for the substance is

[17] BROCKWAY and PALMER, *J. Am. Chem. Soc.*, **59**, 2181 (1937).

[18] DE LAZLO, *Proc. Roy. Soc.* (London), **A146**, 690 (1934).

[19] HÜCKEL, *Z. Physik*, **83**, 632 (1933).

[20] PAULING and WHELAND, *J. Chem. Phys.*, **1**, 362 (1933); **2**, 482 (1934).

(BB) combined, of course, with the usual resonating structures
of the benzene rings. The odd electron is represented by the

(BB)

(CC)
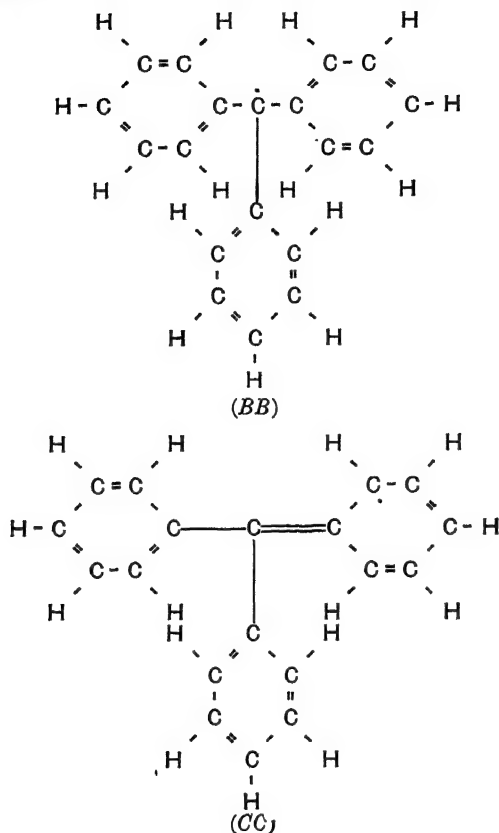
dot on the central carbon atom. But the structure represented
by (CC) is an obvious alternative. This carries the odd electron
on an ortho carbon atom of the right-hand ring and can be
thought of as formed by the rupture of the double bond which
links this atom in (BB) in such a way that one electron remains
on the ortho carbon while the other unites with the odd electron
on the central carbon to form a new double link. There are in
all six equivalent structures with the odd electron on an ortho
carbon atom and three structures with it on a para carbon,
formed by a repetition of the electron shift.

The effect is to spread out over the whole molecule the odd electron, which in a methyl radical or in its saturated derivatives is concentrated on one carbon atom, and to stabilize the structure by virtue of the resonance energy.   The relatively small tendency of triphenylmethyl to associate to the ethane derivative is easily accounted for either in terms of the stabilization of the radical or in terms of the diffusion of the odd electron, which must be concentrated on the methyl carbon in order to form the ethane bond.

This interpretation of the triphenylmethyl problem is supported by the decreased tendency toward association exhibited by triphenylmethyl derivatives in which biphenyl or naphthyl groups have been substituted for phenyl.   These offer a much larger volume through which the odd electron may be diffused and a greater stabilization by virtue of the greater number of resonating structures.   Thus in the biphenyl group one may set up resonating structures with the odd electron on the ortho and para positions of the second phenyl as well as on those of the first.   The existing evidence on the degree of dissociation of

Fig. I-9.—A typical plot of energy against interatomic distance.

various hexaphenylethane derivatives is at least qualitatively in agreement with the predictions that may be derived from the mathematical development of this point of view.[20]

The Interaction of Atoms: Covalent Radii: Bond Angles.— Two atoms that can unite by sharing electrons to form a stable compound interact in a way which is shown schematically in Fig. 9.   The abscissa r represents the distance between centers of the atoms and the ordinate ϕ the potential energy of the system reckoned from a zero value at infinite separation.   As the atoms are brought together, the energy decreases at first, goes through a minimum, then increases rapidly.   Meanwhile, the slope $d\phi/dr$, which measures the force of attraction, increases at first, then decreases and becomes zero at the minimum of the

energy curve. The distance r_m at which the energy is a minimum
and the force zero is the average internuclear distance of the
molecule under zero pressure. At smaller distances the force is
one of repulsion and is very large. The general nature of the
curve is an obvious corollary of the fact that a stable molecule is
formed and that the compressibility of solid and liquid sub-
stances is small. More detailed information has been obtained
from the spectra of gaseous molecules, and the curves are found
to agree satisfactorily with the following empirical equation:[21]

$$\phi = D[e^{-2a(r - r_m)} - 2e^{-a(r - r_m)}] \tag{12}$$

in which D and a are constants.

The distance r_m may be called the *length of the bond*. To a
rather surprising extent these bond lengths are additive functions
of the atoms involved and are constant for atoms of a given
kind. It is therefore possible to write down, as in Table III, a

TABLE III.—COVALENT RADII IN A

Atom	Single bond	Double bond	Triple bond
H	0.30		
C	0.77	0.67	0.60
N	0.70	0.61	0.55
O	0.66	0.57	0.51
F	0.64		
P	1.10		
S	1.04		
Cl	0.99		
Br	1.14		
I	1.33		

set of values of covalent radii, one for hydrogen, one for singly
bound carbon, one for doubly bound carbon, etc., and to calculate
the length of any bond by adding the appropriate radii.[22,8b]
When a bond may be represented as a resonance hybrid of two
types, its length is intermediate between those characteristic of
the two types and may be estimated from a plot of the type of
Fig. 8.

[21] MORSE, *Phys. Rev.*, **34**, 57 (1929).
[22] PAULING and HUGGINS, *Z. Krist.*, **87**, 205 (1934).

The valence angle, which is the angle between the links proceeding from a given atom, shows the same kind of constancy as the bond length. The calculated angle for the bonds of a tetrahedral atom is 109°28', and the valence angle on saturated carbon has been found to have this value in numerous organic molecules. The angle may increase slightly when the atoms attached to carbon are large, the Br—C—Br angle in dibrommethane being 112°.[23] The angle between two atoms bound by single links to olefinic carbon also appears to have nearly the tetrahedral value, being 111 ± 2 deg. in tetramethylethylene.[35] A single link attached to triply bound carbon lies in line with the triple bond; acetylene and hydrogen cyanide are linear molecules.

The H—N—H angle in ammonia is 112 to 116 deg.,[24] corresponding to the pyramidal structure of the molecule (page 15); it would be 120 deg. if the nitrogen lay in the plane of the hydrogens. The H—O—H angle in water is between 104 and 106 deg.; the C—O—C angle in diphenyl oxide is 110 deg.

The interaction of two electrically charged atoms, such as a sodium ion and a chloride ion, must follow a curve of qualitatively the same nature as that of Fig. 9, which must in this case reduce at large distances to the coulombic form $\phi = e_1 e_2 / r$.

The Interaction of Molecules: van der Waals' Forces: Hydrogen Bonding: Other Specific Interactions.—It is a universal property of atoms and molecules to exert relatively weak forces of attraction upon other atoms or molecules. These are called *van der Waals'*, *cohesive*, or *dispersion forces*. They provide an ever-present cohesive force and, in default of stronger forces, are alone responsible for the existence of liquid and solid helium, hydrogen, and methane. In so far as more powerful covalent or coulombic attractive forces do not intervene, the van der Waals' attraction goes over to repulsion at distances that are large compared with the bond lengths of stable compounds. Thus the distance between centers of two hydrogen atoms inside a molecule is 0.75A, but, when two hydrogen atoms are present in different molecules, they are never found to be closer together than 3.0A.[25] Graphite is composed of layers within which the

[23] LEVY and BROCKWAY, *J. Am. Chem. Soc.*, **59**, 1662 (1937).
[24] Ref. 8a, p. 83.
[25] Ref. 8a, p. 48.

carbon-carbon distance is 1.42A, obviously corresponding to covalent bonds (page 25), whereas the distance between layers is 3.33A, corresponding to much weaker van der Waals' forces. The strong binding within the layer together with the weak binding between layers is responsible for the ease of cleavage into thin flakes, which is the most characteristic property of the substance.

Like the distance between atoms inside a molecule, the much larger distance of closest approach of atoms in different molecules is a relatively constant and additive property of the atoms concerned. It is therefore possible to set up, as in Table IV, values of effective atomic radii for interaction between molecules.

TABLE IV.—EFFECTIVE ATOMIC RADII FOR INTERACTION BETWEEN MOLECULES

In A[25]

H	1 0–1.5	F	*ca* 1.4
C	1.67	Cl	1.87
N	1.5	Br	1.85–2.0
O	1.40		

Two molecules the structures of which show marked electrical dissymmetry attract each other by virtue of other and stronger forces in addition to those of van der Waals. In some cases this effect may be treated in terms of the interaction between the electrical dipoles of the molecules; in others a finer analysis is necessary. It has, for instance, been apparent for a long time that molecules containing hydroxyl groups and, to a lesser extent, those containing the NH_2 group cling together especially strongly. The classical statement has been that the substances in question form associated liquids, which meant that their heats of evaporation are higher than those predicted by Trouton's rule and that the surface tension-temperature relationship also deviates from the normal in a way that can be attributed to the presence of powerful intermolecular forces. The coincidence of these phenomena with the presence of hydrogen and of unshared electron pairs in the hydroxyl or amine group suggested the possibility that a hydrogen atom may bond two oxygen or nitrogen atoms,[26] a possibility that has been abundantly confirmed from investiga-

[26] LATIMER and RODEBUSH, *J. Am. Chem. Soc.*, **42**, 1419 (1920).

tions on interatomic distances. Thus the dimer of formic acid has the configuration (DD), and the distance a is equal to 2.67A.[27]

$$
\begin{array}{c}
\text{O - H} \quad\text{O} \\
\diagup \qquad\qquad \diagdown \\
\text{H - C} \qquad\qquad \text{C - H} \\
\diagdown \qquad\qquad \diagup \\
\underbrace{\text{O} \quad \text{H - O}}_{a} \\
(DD)
\end{array}
$$
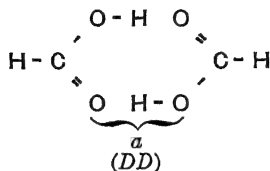
Since the distance would, from Table IV, be 2.80A if the oxygens were in contact, the intervening hydrogen not only occupies no space itself, it even pulls the oxygens closer together. In crystals of oxalic acid dihydrate the distance between the oxygens in the water molecules and the carbonyl oxygens is as low as 2.52A,[28] and similar results have been obtained in the study of other crystalline substances.

A direct diagnostic for the presence of hydrogen bonding has been found[29] in a shift in the frequency of the infrared absorption associated with the vibration of hydrogen relative to oxygen or nitrogen which occurs when the hydrogen is involved in the bonding of two atoms.

The theory of the hydrogen bonding is by no means clear. An early suggestion[26] that hydrogen may have a stable filled shell of four electrons is most improbable, and more recent approaches have been made either from the idea of a resonance between structures in which the hydrogen is linked to the one or the other of the atoms bonded[29] or in terms of a detailed analysis of the electrical fields in the immediate neighborhood of the hydroxyl group.[30] The bonding has somewhat the properties of a true valence, in that a hydrogen atom involved in one hydrogen bond has little tendency to form another. This fact is evidenced by the failure of structures like (DD) to polymerize further and, most interestingly, by the properties of internal hydrogen bonds involving chelation.[31] For instance m- and p-nitrophenols are

[27] PAULING and BROCKWAY, *Proc. Nat. Acad. Sci.*, **20**, 336 (1934).

[28] ROBERTSON, *Proc. Roy. Soc.* (London), **A157**, 79 (1936). ROBERTSON and WOODWARD, *J. Chem. Soc.*, 1817 (1936).

[29] RODEBUSH and BUSWELL, *J. Phys. Chem.*, **43**, 219 (1939).

[30] ONSAGER, *J. Phys. Chem.*, **43**, 189 (1939).

[31] LASSETTRE, *Chem. Rev.*, **20**, 259 (1937).

found by cryoscopic methods to be largely associated in solution in naphthalene, whereas *o*-nitrophenol is unassociated or nearly so. If one assumes that an internal hydrogen bond forms between hydroxyl and nitro groups in the latter case, an impossi-

(*EE*)
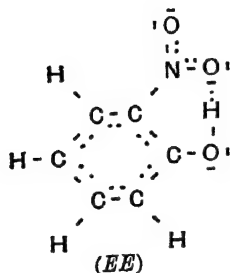
bility for spatial reasons in the other cases, and that this internal bonding prevents the normal external bonding, these phenomena can be accounted for. They are typical of a large variety of similar effects.

There are indications both in the recent work[29] and in earlier work[32] on compound formation between organic molecules that hydrogen bonding is strongest when the hydrogen is most acidic and the oxygen or nitrogen atom to which the bond is made, most basic. In other words, hydrogen bonding between atoms is favored by the same factors that favor the complete transfer of the proton from one atom to the other.

Another type of relatively firm and highly specific bonding between molecules appears in the colored compounds that naphthalene and other aromatic compounds form with picric acid, trinitrobenzene, and the like.[33] The compound formation is favored by electron-attracting groups like CN, SO_2Cl, and CO_2CH_3 in the nitro compound or by an increase in the number of nitro groups present in it, whereas methyl is unfavorable.[33,34] On the other hand, electron-repelling groups like CH_3, OH, and NH_2 favor the compound formation when they are present in

[32] KENDALL, BOOGE, and ANDREWS, *J. Am. Chem. Soc.*, **39**, 2303 (1917).

[33] PFEIFFER, "Organische Molekülverbindungen," Stuttgart, 1922, pp. 218*ff*.

[34] BENNETT and WAIN, *J. Chem. Soc.*, 1108 (1936).

the other component.   This may be interpreted to mean that a low electron density on the nitro group and a high one on the unsaturated linkages of the other component are essential factors in the interaction.[34]   A quantitative theory has also been approached[35] in terms of the polarization of the loosely bound electrons of the aromatic compound by the strong dipole of the nitro group.

[35] BRIEGLEB, *Z. physik. Chem.*, **B26,** 63 (1934); **B31,** 58 (1935).

CHAPTER II

STRUCTURAL THEORY: ELECTROLYTES

The Applicability of Structural Methods.—One of the most striking evidences of the reliability of the organic chemist's methods of determining molecular structure is the fact that he has never been able to derive satisfactory structures for supposed molecules which are in fact nonexistent. For instance, the question of whether the potassium in potassium cyanide is linked to carbon or to nitrogen used to be the subject of much discussion; it was never settled and is now known to have had no meaning. The substance consists of equal numbers of potassium and cyanide ions. In solution these are independent entities; in the solid state they are stacked up in a three-dimensional chessboard identical with that which is now so familiar in the case of sodium chloride. Each cyanide ion is at the center of a group of six equidistant potassium ions, one in front, one in back, one to the right, one to the left, one up, one down. In the same way, each potassium ion is at the center of a similar group of cyanide ions. Neither in solution nor in the crystal is there anything that can by any right be called a molecule of potassium cyanide, and the futility of attempting to determine the structure of such a molecule is now obvious. The potassium ion is linked neither to carbon nor to nitrogen; it is merely the positive ion which must be present in an amount equivalent to that of the negative cyanide ions. For the same reason, such "structural" formulas as

$$
\begin{array}{cccc}
& O & O & O & H\ H \\
& \nearrow & \nearrow\ \searrow & \nearrow & \searrow\ | \\
Na-O-N & Ca & C=O & Na-O-C & H-N-Cl \\
& \searrow & \searrow\ \nearrow & \searrow & | \\
& O & O & H & H
\end{array}
$$
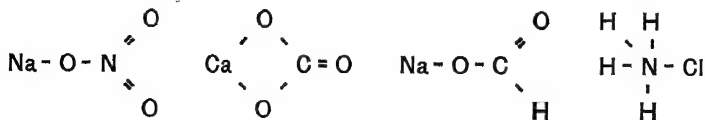
are completely meaningless. In all these cases the crystals have ionic lattices, *i.e.*, alternating arrangements of fundamentally the same sort as sodium chloride or potassium cyanide.

38

The Nature of Salt Crystals: Solubility of Salts.—The properties of salt crystals may be satisfactorily interpreted as the result primarily of the forces between the ions. The repulsion due to the like charged ions is weaker than the attraction due to those of unlike charge, because the like charged ones are on the average farther apart. Because the electrical forces are powerful, such crystals have high cohesion and are mechanically strong. Because they also resist the breaking down involved in fusion, evaporation, or solution, salts tend to have high melting and boiling points and to be insoluble in most solvents. Many of them do dissolve in water and to a lesser extent in a few other solvents (page 40). In the process of solution the crystal breaks down into the ions that are its building stones; a factor of great importance in this breakdown is the high dielectric constant of the solvent. The work required to separate two unlike charges varies inversely as the dielectric constant of the medium, and, even though actual ions do not behave exactly like point charges, the work required to break down an ionic lattice in water with a dielectric constant of 80 must be not far from one-eightieth of that required in a vacuum. A high dielectric constant is a necessary, but apparently not a sufficient, condition for a "good salt solvent," since liquid hydrogen cyanide with a dielectric constant of 116 at 20° dissolves very few salts in appreciable amounts.[1] In order that salts may dissolve, a considerable tendency on the part of the solvent molecules to attach themselves to the ions, to solvate them, appears to be necessary. The mechanism of the solvation and the necessary conditions for its appearance are not known with certainty, but it is a striking fact that hydroxyl derivatives, *viz.*, water, the alcohols, and the organic acids, are the best salt solvents and that ammonia and the amines follow. Increase in the size of a hydrocarbon residue in the solvent is always unfavorable. In all these respects, ability to dissolve salts runs parallel with tendency toward association of the hydrogen-bonding type (page 34). This perhaps indicates that the solvation depends upon hydrogen bonding between the solvent molecules and the unshared electrons of the anions of the salt. The best solvents that do not contain hydroxyl or amine hydrogen are nitromethane

[1] FREDENHAGEN and DAHMLOS, *Z. anorg. allgem. Chem.*, **179**, 77 (1929).

and sulfur dioxide, although they lag considerably behind hydroxyl compounds of equal dielectric constant. Sulfur dioxide is known to form solvate compounds with the halide ion,[2] perhaps because the sulfur carries only a sextet of electrons and may attach itself to the lone pairs of the halide ion. Halogen compounds like chloroform and ethylene chloride are better solvents than hydrocarbons.[3] These rules are very general and approximate; the solubility of any salt in any solvent is ultimately a specific property of the combination. Thus silver fluoride is readily soluble in water, and silver iodide is the least soluble of the halides; in liquid ammonia the fluoride is difficultly soluble, the iodide extremely soluble.[4]

Ion Pairs, Triplets, Etc.—The breakdown of the crystal into ions on solution need not be complete. It is probable that even aqueous solutions of ionic substances contain ion pairs, *i.e.*, pairs of ions of opposite charge held together by the electrostatic attraction due to their charge,[5] but the concentration is so low that it is difficult to establish their presence with certainty. They are, however, easily shown to be present in liquid ammonia, and the proportion becomes large in solvents of low dielectric constant. There is a group of electrolytes consisting of large organic ions that dissolve even in the most unfavorable solvents. Salts like tetraamylammonium picrate or sodium triphenylmethide dissolve appreciably in ether, dioxane, or ethylene chloride, and some of them even dissolve measurably in benzene. In these solutions a wide variety of association products have been found to be present.[6] If M^+ represents the cation and A^- the anion, it appears that ion pairs MA, triplets MAM^+ and AMA^-, and probably still more complex groupings are present. The proportion of free ions may be small, being of the order of 10^{-8} to 10^{-10} for quaternary ammonium salts in benzene.

[2] JANDER and MESECH, *Z. physik. Chem.*, **183**, 121 (1938).

[3] There is much information on the solubilities of salts in various solvents in the work of Walden, summarized in his book, "Salts, Acids and Bases; Electrolytes; Stereochemistry," New York, 1929.

[4] FREDENHAGEN, *Z. anorg. allgem. Chem.*, **186**, 1 (1930).

[5] BJERRUM, *Kgl. Danske Videnskab. Selskab.*, Math.-fys. Medd. [9], **7**, 1 (1926).

[6] FUOSS, *Chem. Rev.*, **17**, 27 (1935).

In spite of the fact that the ion pair is a molecule of the salt, it is impossible to write a useful structural formula for it. The structural formula is based upon and indissolubly bound up with the concepts of definite linkages and of valence forces that exhibit the property of saturation. These characteristics are those of shared-electron bonds; the electrostatic attraction involved in the formation of the ion pairs behaves in an entirely different fashion (page 12). There is no saturation of valence, no definite linkage between the atoms in the different ions; the ion pair is merely one of a large number of equally important intermediates between ion and crystal.

The Molecular Structure of Ions: The Werner Principle.— The structure of an organic ion, within which the linkages are of the shared-electron kind, is just as definite a thing as that of a neutral molecule. Its determination rests fundamentally upon the same principles and the same methods of investigation as those which apply to neutral molecules. The possibility of determining by chemical methods the structure of an ion and the impossibility of determining the structure of the molecule of an electrolyte were recognized by Werner as early as 1893[7] and form the basic principles that he used in his extraordinarily successful attack on the problem of the inorganic complex compounds.

Pseudo-electrolytes: Acids and Bases.—In contrast with salts there is a group of substances which are not inherently electrolytes but which are converted to electrolytes by definite chemical reactions when they are dissolved in suitable solvents. The best known of these are the acids and bases. Thus hydrogen chloride is a low-boiling, low-melting substance that is practically a nonconductor in the pure liquid state or in solution in benzene. Yet it is, for all practical purposes, completely converted to ions in dilute aqueous solution. It is overwhelmingly probable that the ionization involves the reaction

$$\mathrm{H-\overset{..}{\underset{..}{O}}-H + H-\overset{..}{\underset{..}{C}l\,\cdot} \rightleftharpoons \left[\mathrm{H-\overset{..}{O}-H}\atop{\overset{|}{\mathrm{H}}}\right]^{+} + [\,\cdot\,\overset{..}{\underset{..}{C}l}\,\cdot\,]^{-} \qquad \textbf{(I)}$$
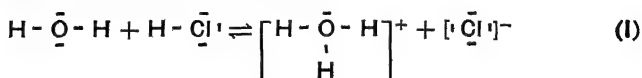
The ion OH_3^+ is called *oxonium ion*, sometimes also *hydronium* or *hydroxonium ion*. Reactions like this, which consist in the

[7] WERNER, *Z. anorg. allgem. Chem.*, **3**, 267 (1893).

transfer of a proton, are called *protolytic*, and this theory of the ionization of acids and bases is the *proton-transfer theory of acids and bases*. Some of the most important evidence for it follows.

The theory accounts for the contrast between the properties of hydrogen chloride in aqueous solution on the one hand and in the pure state or in benzene solution on the other. It avoids the difficulty of supposing that the solution contains free hydrogen ions. Unlike sodium or chloride ions, these are bare nuclei; they are much smaller than the other ions and are surrounded by much more intense fields of force. Consequently, they must either tear electrons from other atoms or molecules or share electrons with them, they cannot exist uncombined.[8]

No one doubts that the ionization that occurs when hydrogen chloride is dissolved in liquid ammonia is due to the proton-transfer reaction

$$NH_3 + HCl \rightleftharpoons NH_4^+ + Cl^- \tag{II}$$
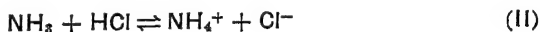
because the salt NH_4Cl may be obtained by evaporating the solvent. The chief difference between this reaction and that of equation (I) is that the greater positive charge on the oxygen nucleus hinders the transfer so that it has less tendency to occur and more to be reversed. Oxygen compounds are for this reason less basic than the corresponding nitrogen derivatives. In other respects the effects of equation (I) in aqueous HCl and of equation (II) in ammoniacal HCl are very similar. This fact appears in notable fashion in that ammonium salts in ammonia have all the properties traditionally characteristic of acids. They act on metals with the evolution of hydrogen; they neutralize amides, which are the ammonia analogues of the hydroxides in aqueous solution; they change the color of indicators; they catalyze reactions (page 52); and they dissolve salts of weak acids in just the same way that acids do in water.[9]

The certainty that chemists feel about the existence of ammonium salts derives from the fact that so many of them are known in the solid state, are obviously saltlike in all their properties, and have been found to possess an ionic lattice. Yet all of them

[8] Brønsted, *Ber.*, **61B**, 2049 (1928).

[9] Franklin, "The Nitrogen System of Compounds," New York, 1935.

break down into nonionic fragments by the reversal of reaction (II) at slightly elevated temperatures; the vapor of ammonium chloride contains no detectable quantity of ammonium chloride molecules but consists of ammonia and hydrogen chloride.[10] By reason of the lower basicity of oxygen, the oxonium salts break down at a lower temperature, but the difference is one of degree, not one of kind, and the oxonium salts of the stronger acids are relatively stable. Thus the crystalline monohydrate of perchloric acid has been shown by X-ray methods [11a] to consist of the ions OH_3^+ and ClO_4^-. It is really a salt and should be called oxonium perchlorate. Similarly, the dihydrate of boron fluoride[11b] consists of the ions OH_3^+ and BF_3OH^-. The same thing is no doubt true, although not yet directly demonstrated, for the hydrates of many of the strongest acids, notably for the stable hydrates of the sulfonic acids, the properties of which are very different from those of the anhydrous acids.

The formation of stable saltlike reaction products by the reaction of strong acids with organic oxygen compounds was first observed in 1899[12] in the case of dimethylpyrone. The phenomenon has been found to be very general and is especially important with the anthocyanins, naturally occurring coloring matters. These oxonium salts were at first said to be examples of "quadrivalent oxygen," but the term was used in the same sense in which the nitrogen in ammonium salts was at that time called *quinquevalent;* it was recognized that the "fourth valence" of the oxygen is an ionic one.[13] Although the terminology of that day was different, the process visualized for the salt formation was essentially that of equation (I).

The early workers on oxonium salts recognized that the most direct evidence for the analogy between oxonium and ammonium salts would be the isolation of the tertiary oxonium salts which are the analogues of the quaternary ammonium salts. The problem is a difficult one since the tendency to decompose by reaction (III) is inevitably large. It has only recently been

[10] RODEBUSH and MICHALEK, *J. Am. Chem. Soc.*, **51**, 748 (1929).

[11] (*a*) VOLMER, *Ann.*, **440**, 200 (1924). (*b*) KLINKENBERG and KETELAAR, *Rec. trav. chim.*, **54**, 959 (1935).

[12] COLLIE and TICKLE, *J. Chem. Soc.*, **75**, 710 (1899).

[13] BAEYER and VILLIGER, *Ber.*, **34**, 2679 (1901).

$$\left[H_3C - \bar{O} - CH_3 \right]^+ + X^- \rightleftharpoons H_2C - \underset{\cdot}{\bar{O}} - CH_3 + H_3CX \qquad \text{(III)}$$
$$\qquad\qquad \underset{CH_3}{|}$$
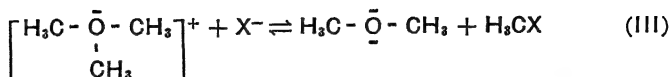
solved[14] by the preparation of a substance the saltlike properties and composition of which indicate that it is the fluoborate of the expected trimethyloxonium ion (*A*)

$$\left[\underset{H_3C - \underset{\cdot}{O} - CH_3}{\overset{CH_3}{|}} \right]^+ \left[\underset{\cdot F\cdot}{\overset{\cdot \bar{F} \cdot}{\underset{\cdot}{|}}} \bar{F} - B - \bar{F}\cdot \right]^-$$

(*A*)
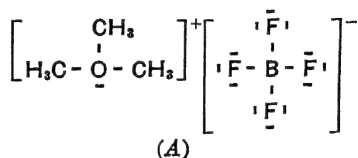
The corresponding dimethylethyloxonium and triethyloxonium compounds have been isolated as well as the triethyloxonium picrate.

Some very beautiful and significant experiments in which the solvent was sulfur dioxide were reported in 1920.[15] Besides being a relatively good solvent for electrolytes, this solvent is not acidic and is only weakly basic. The solubility of water is very small, hydrogen bromide is soluble but not appreciably ionized; yet a solution of hydrogen bromide dissolves precisely one mole of water for every mole of hydrogen bromide, and the solution is an excellent conductor. There could be no more direct evidence of the reaction

$$HBr + H_2O \rightleftharpoons OH_3^+ + Br^- \qquad \text{(IV)}$$
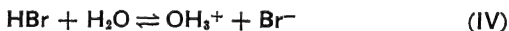
When the solution is electrolyzed, water is set free at the cathode by the discharge of the oxonium ion. By isolating and weighing the water, it was found that one mole is liberated for each faraday, in accordance with the equation

$$OH_3^+ + e \rightleftharpoons H_2O + H \qquad \text{(V)}$$

Equations (I) and (II) are as much representations of the ionization of the bases water and ammonia as they are of that of the acid hydrogen chloride. When a little acid is dissolved in a basic solvent, one speaks of the ionization of the acid; when a

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[14] MEERWEIN, HINZ, HOFMANN, KRONING, and PFEIL, *J. prakt. Chem.* (II), **147**, 257 (1937).

[15] BAGSTER and COOLING, *J. Chem. Soc.*, **117**, 693 (1920).

small amount of base is present in an acidic solvent, one refers to the ionization of the base. The difference is one of convenience only. Ammonia ionizes in water by the reaction

$$NH_3 + H_2O \rightleftharpoons NH_4^+ + OH^- \tag{VI}$$
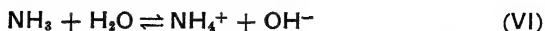
The name ammonium hydroxide, often given to a solution of ammonia in water, implies only the presence of ammonium and hydroxyl ions. There is, it is true, a compound of ammonia and water, the existence of which is probably due to hydrogen bonding. But this melts with decomposition at $-79.3°c$, and the amount present in aqueous ammonia can hardly be important.

Solutions in Sulfuric Acid: Very Weak Bases.—In order to investigate the ionization of very weak bases, one must turn to a solvent that is less basic than the solutes, otherwise the solvent molecules capture practically all the available protons. The widest step available in this direction is the use of sulfuric acid as the solvent.[16] This has very desirable properties for the purpose; interionic forces are small, presumably because of an extremely high dielectric constant, although this has never been measured. Consequently, the freezing-point depression per mole produced by a binary electrolyte is almost exactly twice as great as that produced by a nonelectrolyte, instead of being as in water 1.8 to 1.9 times as great. It freezes at a convenient temperature $(10.5°c)$ for cryoscopic measurements, and it is relatively cheap and available in high purity. There are minor complications owing to the large ionization of the solvent which have delayed a complete understanding of the system, but these effects are easily eliminated.[16e]

The freezing-point depression per mole of a nonelectrolyte is known, both from the familiar relation between heat of fusion and cryoscopic constant and from cryoscopic measurements on substances (trichloracetic acid, picric acid, dinitrobenzene) that do not conduct when dissolved in sulfuric acid, to be 6.154 deg./mole. $NaHSO_4$ and other alkali bisulfates conduct and yield freezing-point depressions of 12 to 13 deg./mole, which can

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[16] (a) HANTZSCH, *Z. physik. Chem.*, **61**, 257 (1908). (b) HANTZSCH, *ibid.*, **65**, 41 (1908). (c) HANTZSCH, *Ber.*, **55B**, 953 (1922). (d) HANTZSCH, *ibid.*, **63B**, 1782; 1789 (1930). (e) HAMMETT and DEYRUP, *J. Am. Chem. Soc.*, **55**, 1900 (1933). (f) HAMMETT and LOWENHEIM, *ibid.*, **56**, 2620 (1934). (g) TREFFERS and HAMMETT, *ibid.*, **59**, 1708 (1937).

mean only that one mole of salt furnishes two moles of solute to the solution, one of sodium ion and one of bisulfate ion. Water yields the same molar freezing-point depression, and this can be only because by way of the reaction

$$H_2O + H_2SO_4 \rightleftharpoons OH_3^+ + HSO_4^- \qquad (VII)$$
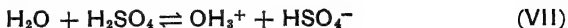
one mole of water gives rise to one mole each of oxonium ion and bisulfate ion. A wide variety of organic oxygen compounds yield the same molar depression as water, are conducting solutes, and may be recovered unchanged by addition of water to their solution in sulfuric acid. They must therefore react in the same way as water. The list includes ethers, esters, ketones, aldehydes, and acids, and typical reactions are

$$(C_2H_5)_2O + H_2SO_4 \rightleftharpoons [(C_2H_5)_2OH]^+ + HSO_4^- \qquad (VIII)$$
$$C_6H_5 - CO - CH_3 + H_2SO_4 \rightleftharpoons [C_6H_5 - COH - CH_3]^+ + HSO_4^- \quad (IX)$$
$$CH_3COOH + H_2SO_4 \rightleftharpoons [CH_3C(OH)_2]^+ + HSO_4^- \qquad (X)$$
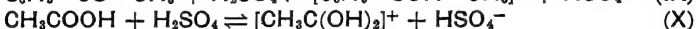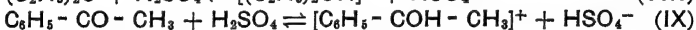
The behavior of the chloracetic acids effectively verifies this interpretation of the ionization process. Monochloracetic acid, like acetic acid itself, gives a twofold depression and is therefore completely ionized [equation (X)]. Dichloracetic acid gives a depression between one and two times that of a nonelectrolyte and is therefore partly ionized. Trichloracetic acid is a nonelectrolyte. This is exactly the predicted behavior; substitution of chlorine for hydrogen increases the tendency of the acid RCO_2H to lose a proton, and it should consequently decrease its tendency to accept a proton. With one chlorine the substance is still a strong base in sulfuric acid, with two it is weak but measurably basic, with three the basicity is no longer detectable.

Even inorganic acids may act as bases under conditions of sufficiently high acidity. HNO_3 gives somewhat more than a twofold depression in sulfuric acid,[16a] its solution is conducting, and the light absorption is entirely different from that of molecular nitric acid or of nitrate ion.[17] Furthermore, stable compounds of nitric acid with $H_2S_2O_7$ and with $HClO_4$ have been isolated, which conduct when dissolved in nitromethane and have been shown by transference experiments in that solvent to contain the nitrogen in the cation. Their compositions correspond to the structures (B), (C), and (D)

[17] HANTZSCH, *Ber.*, **58**, 941 (1925).

$$\left[\,\underline{|}\underline{\text{O}}=\text{N}\begin{array}{c}\overset{\overset{\bar{}}{\text{O}}\text{-H}}{}\\ \\ \underset{}{\underline{\text{O}}\text{-H}}\end{array}\right]^{+}\ \text{HS}_2\text{O}_7{}^{-}$$

(B)

$$\left[\,\underline{|}\underline{\text{O}}=\text{N}\begin{array}{c}\overset{\overset{\bar{}}{\text{O}}\text{-H}}{}\\ \\ \underset{}{\underline{\text{O}}\text{-H}}\end{array}\right]^{+}\text{ClO}_4{}^{-}$$

(C)

$$\left[\,\text{H-}\underline{\bar{\text{O}}}\text{-N}\begin{array}{c}\overset{\overset{\bar{}}{\text{O}}\text{-H}}{}\\ \\ \underset{}{\underline{\text{O}}\text{-H}}\end{array}\right]^{++}\ (\text{ClO}_4{}^{-})_2$$

(D)
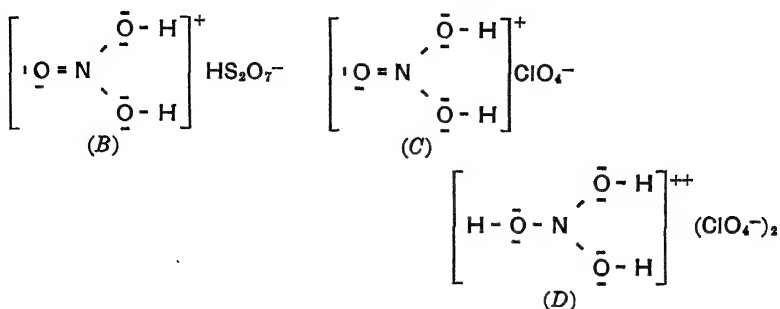
Similarly, evidence for the basicity of phosphoric acid has been obtained through the compound $[\text{P(OH)}_4]^+[\text{ClO}_4]^-$.[18]

The following substances have been found to be simple monoacid bases the ionization of which according to an equation of the type of (VII) to (X) is practically complete: ethyl ether; ethyl acetate; acetophenone; benzophenone; benzalacetophenone; benzil; anthraquinone; dimethylpyrone; acetaldehyde; acetic chloracetic, and trimethylacetic acids; benzoic acid and its *p*-brom, *p*-nitro, *o*-methyl, 2,4-dimethyl, 2,4,5-trimethyl, 3,4,5-trimethoxy, and 2-methyl-6-nitro derivatives; malonic, fumaric, and isophthalic acids; many nitroanilines, including the trinitro compound, azobenzene and its *p*-nitro derivative; acridine; acetonitrile; tolunitrile; benzamide; cyanuric acid.

Dichloracetic acid and nitrobenzene are incompletely ionized; HCl and HF are reported in the same class.

The following are soluble but not measurably ionized: trichloracetic acid, trifluoacetic acid, picric acid, phthalic anhydride, dimethyl sulfate, trinitrobenzene and trinitrotoluene, dinitrobenzene, nitromethane, benzene sulfonic acid and its *m*-nitro derivative, methane and ethane sulfonic acids, perchloric acid.

Methyl and ethyl alcohols are converted to alkylsulfuric acids, the presence of which may be demonstrated by dilution with water and suitable tests.   By the reaction

$$\text{CH}_3\text{OH} + 2\text{H}_2\text{SO}_4 \rightarrow \text{CH}_3\text{SO}_4\text{H} + \text{OH}_3{}^+ + \text{HSO}_4{}^- \qquad \text{(XI)}$$
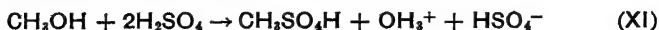
the depression is three times that of a nonelectrolyte.   Phthalic, succinic, and maleic acids give similar depressions, probably by way of anhydride formation.   Urea, hydrazine dicarboxylic

[18] ARLMAN, *Rec. trav. chim.*, **56**, 919 (1937).

ester, and some other nitrogen compounds appear to be able to add two protons, giving a threefold depression. Triphenyl-carbinol and some other substances give a fourfold depression by way of the formation of a carbonium ion (page 54).

Nomenclature : The Brønsted-Lowry Terminology.—The existence of this large variety of positive ions poses a problem in nomenclature for which the standard terminology of structural organic chemistry has no satisfactory answer. In terms of a widely accepted suggestion of Brønsted[19] and Lowry[20] the cations formed in equations (VIII) to (X) may be denoted simply as the conjugate acids of ether, acetophenone, and acetic acid, respectively.

In this terminology any substance that can accept a proton by virtue of an unshared electron pair is a base, and the product formed by the addition of a proton to a base is an acid. An acid and a base that are related in this way are said to be *conjugate* or corresponding. The classification does not depend upon charge; ammonium ion, NH_4^+, acetic acid, $HC_2H_3O_2$, and bisulfate ion, HSO_4^-, are acids, the conjugate bases of which are ammonia, NH_3, acetate ion, $C_2H_3O_2^-$, and sulfate ion, SO_4^-, respectively.

The nomenclature has given rise to some confusion because it uses the familiar words acid and base in a new sense. This has happened before in the history of these words, as it has with many of the words that scientists use. The Arrhenius-Ostwald definition of an acid as a substance that ionizes to produce hydrogen ion and of a base as one that ionizes to produce hydroxyl ion is by no means identical with the previously accepted definitions and is itself of no great antiquity. Indeed, many practical chemists have refused to accept the precisian's insistence that anilinium hydroxide not aniline is the base and now find the fashion veering back in their direction. With. the Brønsted-Lowry nomenclature now approaching general acceptance, it is to be hoped, however, that no further immediate changes will be made.

The strongest acids must be conjugate to the weakest bases, *i.e.*, when an acid possesses weakly bound protons the loss of a

[19] Brønsted, *Rec. trav. chim.*, **42**, 718 (1923).
[20] Lowry, *Chem. and Ind.*, **42**, 43 (1923).

proton forms a base with little affinity for protons.   In terms of the proton-transfer theory (page 42) the typical reactions of acids and bases consist in the transfer of a proton from an acid to a base.   Familiar examples are the ionizations of equations (I) and (VI), neutralization, *e.g.*,

$$OH_3^+ + OH^- \rightleftharpoons 2H_2O \tag{XII}$$

and hydrolysis, *e.g.*, .

$$H_2O + C_2H_3O_2^- \rightleftharpoons OH^- + HC_2H_3O_2 \tag{XIII}$$
$$NH_4^+ + C_2H_3O_2^- \rightleftharpoons NH_3 + HC_2H_3O_2 \tag{XIV}$$
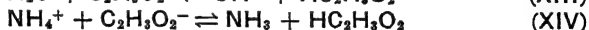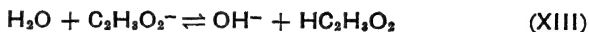
In all these cases an acid transfers a proton to a base, the reaction products being the acid and base conjugate to the reactants.

The Study of Very Weak Acids.—The investigation of very weak acids requires a solvent of still weaker acidity.   Liquid ammonia has proved very useful for this purpose, and a solution in it of the strong base amide ion, NH_2^-, *i.e.*, potassium amide, suffices to convert a number of hydrocarbons to their conjugate bases.[21]   Triphenylmethane reacts

$$(C_6H_5)_3CH + NH_2^- \rightleftharpoons (C_6H_5)_3C^- + NH_3 \tag{XV}$$
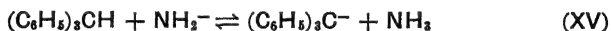
to form an intensely red *carbanion*, as does diphenylmethane but not toluene.   In ether the same hydrocarbons react with alkali metals to form conducting solutions with the same intense colors[22]

$$(C_6H_5)_3CH + K \rightarrow (C_6H_5)_3C^- + K^+ + \tfrac{1}{2}H_2 \tag{XVI}$$
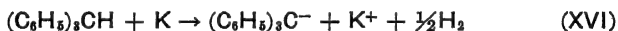
Ether solutions of such carbanions have been used to demonstrate the acidity of many very weakly acidic substances and even to measure approximately their acid strengths.[23]   This was accomplished by observing, either by the color change or by a chemical method, the extent of the reaction of one acid with the carbanion of another.   The equilibrium constant of the reaction

$$HA_1 + A_2^- \rightleftharpoons A_1^- + HA_2 \tag{XVII}$$

[21] KRAUS and ROSEN, *J. Am. Chem. Soc.*, **47**, 2739 (1925).   WOOSTER and MITCHELL, *ibid.*, **52**, 688 (1930).

[22] SCHLENK and MARCUS, *Ber.*, **47**, 1664 (1914).

[23] (*a*) CONANT and WHELAND, *J. Am. Chem. Soc.*, **54**, 1212 (1932).   (*b*) McEWEN, *ibid.*, **58**, 1124 (1936).

thus determined measures the relative strength of the acids HA_1 and HA_2. Table I lists the substances studied in the order

TABLE I.—STRENGTH OF VERY WEAK ACIDS[23]

pK_a	Substances
14–15	N-Methyletioporphyrin
16	Methanol, etioporphyrin
16.5	2,4-Dimethyl-3,5-dicarbethoxypyrrole
18	Ethanol, i-propyl alcohol, benzyl alcohol, benzhydrol
19	t-butyl alcohol, t-amyl alcohol, triphenylcarbinol, menthol, acetophenone
21	Phenylfluorene, α-naphthylfluorene, phenylacetylene, indene
23	Diphenylamine
25	Fluorene
27	Aniline, p-toluidine, p-anisidine
29	Xanthane, phenylxanthane
31	Diphenylbiphenylmethane
33	Triphenylmethane
34	Diphenyl-α-naphthylmethane
35	Diphenylmethane
36	Diphenylmethylethylene
37	Cumene

of decreasing acid strength, together with an estimate on an arbitrary scale of the pK_a values.

The Differentiation of Ion Association Products from True Molecules.—The behavior of sodium triphenylmethide and similar substances brings up the question whether it is possible in practice to distinguish ion pairs and other electrostatic polymers from molecules in which all the linkages are due to electron sharing. Ion association in these ether solutions is so extensive[24] that the "degree of dissociation" of the salt is of the order of 10^{-5}; salts may therefore be just as weak electrolytes as acids or bases.

A distinction is possible when crystal-structure data are available; a substance with an ionic lattice is a salt, and its component ions are bound by electrostatic forces; one with a molecular lattice is either a nonelectrolyte or a pseudo-electrolyte, and its atoms are linked by valence forces. One may also consider other less definite properties and look for the presence or absence of such typical salt properties as high melting and boiling points and insolubility in solvents of low dielectric

[24] KEEVIL and BENT, *J. Am. Chem. Soc.*, **60**, 193 (1938).

constant.   Unfortunately, however, salts containing large organic ions tend to approach the properties of nonelectrolytes in these respects, so that this diagnostic must be used with caution.

The color and more generally the light absorption in the visible or ultraviolet permit an unambiguous distinction in many cases. The formation of an ion pair by electrostatic attraction, and without the appearance of new valence links, has very little effect upon the light absorption of a molecular species because it does not vitally affect the electronic structure.[25]   A familiar example is the identity of the color of the hydrated copper ion in crystalline copper sulfate hydrate and that of the same ion in dilute aqueous solution.   On the other hand, the formation of a new valence link produces in most cases, although not always,[26] a large change in absorption.   This involves a change in color if the absorption happens to lie in the region of visible light, but the change is just as definite and recognizable when it is in the ultraviolet.   In the case of triphenylmethane and its salts, the sodium and potassium compounds have identical colors, and the color is the same in ether solution in which the ionization is minute as it is in ammonia in which the concentrations of free ions and polymers are comparable.[27]   Consequently, the light absorption of the ion must be practically identical with that of the ion pairs which it forms both with sodium and with potassium ion.   But when the ion is converted to triphenylmethane with formation of a new C—H bond, the absorption shifts to the ultraviolet and the substance is colorless.

In the case of picrate ion the most accurate measurements[28a] have shown only minute differences between the absorption of the ion and the ion pairs that it forms with alkali ions.   Here also the formation of the new valence link when the ion is converted to picric acid shifts the absorption into the ultraviolet. The yellow color of solid picric acid is due to impurities, such as ammonium and oxonium picrates, the molecular acid is colorless.

[25] HANTZSCH, *Ber.*, **50**, 1422 (1917); **60B**, 1933 (1927).

[26] FLEXSER, HAMMETT, and DINGWALL, *J. Am. Chem. Soc.*, **57**, 2103 (1935).

[27] KRAUS and KAHLER, *J. Am. Chem. Soc.*, **55**, 3537 (1933).

[28] (a) VON HALBAN and SZIGETI, *Helv. Chim. Acta*, **20**, 746 (1937).   (b) KRAUS, *J. Phys. Chem.*, **43**, 231 (1939).

Another significant difference between ion pairs and valence compounds appears in the fact that a series of organic anions, R_1^-, R_2^-, R_3^-, etc., differ much less in the extent to which they combine with a given metallic ion to form the ion pairs R_1Na, R_2Na, R_3Na, etc., than in the extent to which they are converted to R_1H, R_2H, R_3H, etc., at a given acidity.[23b,24] The extent of ion association is in fact nearly constant if the nature of the atom or group of atoms on which the ionic charge is concentrated remains constant;[23b] the tendency to form valence links may vary greatly.

The formation of ion pairs may also have very little effect upon the chemical reactivity of an ion. The catalytic effect of the ammonium ion, which involves a protolytic reaction of the ion, has a range of variation from 0.0386 to 0.0492 in 0.1N solutions in liquid ammonia of ammonium acetate, chloride, bromide, nitrate, iodide, perchlorate, formate, benzoate, and thiocyanate. The degree of dissociation of the ion pairs varies from 0.04 to 0.474, and there is not even any parallelism between the small variations in the one case and the large variations in the other.[29]

In the light of such considerations as these, it is profitable to distinguish between *ionization* and *dissociation*. The ionization of an electrically neutral acid or base consists in its conversion to ions by a protolytic reaction. The ions thus produced constitute a salt, which may be more or less dissociated. In the case just cited all the acids from acetic to perchloric are completely ionized in liquid ammonia; the dissociation of the ammonium salts formed by the ionization is incomplete and varies from case to case.

The Necessary Conditions for the Ionization of an Acid or a Base.—Ionization depends upon an opposition of properties between solvent and solute. Ammonia is a weak base in water, reaction (VI) occurring to the extent of 1 per cent or so ($K = 1.8 \times 10^{-5}$). In the more acid solvents formic, acetic, or sulfuric acids, its ionization is practically complete, the reactions being of the type

$$NH_3 + RCOOH \rightleftharpoons NH_4^+ + RCOO^- \qquad (XVIII)$$

[29] SHATENSHTEIN, *Acta Physicochem. U.R.S.S.*, **3**, 37 (1935); *J. Am. Chem. Soc.*, **59**, 432 (1937).

Water is a much weaker base than ammonia, its ionization in formic acid

$$H_2O + HCOOH \rightleftharpoons OH_3^+ + HCOO^- \qquad (XIX)$$

taking place to about the same extent ($K = 1.7 \times 10^{-5}$) as that of ammonia in water.[30]   In the more acidic solvent sulfuric acid, its ionization [equation (VII)] is practically complete.   Hydrogen chloride is a strong acid in water, reaction (I) being practically complete.   In the less basic solvent formic acid, its ionization is incomplete although considerable;[31] in sulfuric acid, it probably ionizes as a base (page 47).

Carbonium Ions.—Triphenylmethyl chloride is the type of another class of pseudo-electrolytes.   The substance is colorless and soluble in organic solvents, yielding solutions which in the case of chloroform, benzene, and ethyl acetate are colorless and nonconducting.   Yet its solutions in sulfur dioxide are intensely yellow and are excellent conductors.[32]   Solutions in cresol show strong absorption in the same spectral region as those in sulfur dioxide, and their conductance, although not large, is unmistakable.[33]   In a solvent with so low a dielectric constant (5.0), ion association is of course extensive.   Solutions in nitromethane, nitrobenzene, and acetone show a similar although weaker light absorption.   This behavior is typical of a pseudo-electrolyte, the ionization of which by rupture of a shared-electron bond involves an extensive rearrangement of the electronic system and a consequent change in absorption and which ionizes only under the influence of specific solvents.

The function of the solvent bears no relation to dielectric constant, as the large ionization in cresol amply demonstrates. Its nature is strongly indicated by the fact that ionization can be induced, as evidenced both by color and by conductivity, by the addition to a colorless solution in a nonionizing solvent of such substances as $SnCl_4$ or $AlCl_3$.[34]   These metallic chlorides

[30] HAMMETT and DEYRUP, *J. Am. Chem. Soc.*, **54**, 4239 (1932).

[31] SCHLESINGER and CALVERT, *J. Am. Chem. Soc.*, **33**, 1924 (1911). SCHLESINGER and MARTIN, *ibid.*, **36**, 1589 (1914).

[32] WALDEN, *Ber.*, **35**, 2018 (1902).

[33] HANTZSCH, *Ber.*, **54**, 2573 (1921).

[34] NORRIS and SANDERS, *Am. Chem. J.*, **25**, 54 (1901).   GOMBERG, *Ber.*, **34**, 2726 (1901).   KEHRMANN and WENTZEL, *ibid.*, **34**, 3815 (1901).

are themselves nonelectrolytes in the absence of water or alcohols but possess a pronounced affinity for chloride ion with which they react to form complex ions such as $SnCl_6^=$ and $AlCl_6^≡$. Their effect upon the organic chloride is clearly to remove a chloride ion from it:

$$(C_6H_5)_3CCl + SnCl_4 \rightleftharpoons (C_6H_5)_3C^+ + SnCl_5^- \qquad (XX)$$
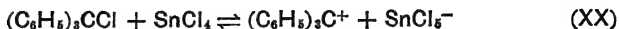
The process is of the same sort as the ionization of an acid or base, except that a chloride ion is transferred instead of a hydrogen ion. The positively charged carbon compound is called a *carbonium* ion, the one formed in equation (XX) being triphenylcarbonium ion.

It is probable that the solvents in which triphenylmethyl chloride ionizes act upon it in the same way that the metal chlorides do. Thus the addition of sulfur dioxide to a chloroform solution of triphenylmethyl chloride leads to ionization in just the same way as does the addition of $SnCl_4$.[33] Most of the effective solvents are hydroxylic substances the molecules of which can form hydrogen bonds with the unshared electrons on the chloride ion. Sulfur dioxide also is known to solvate halide ions (page 40). Molecular HCl can also induce ionization; for colorless trianisylmethyl chloride reacts with dry hydrogen chloride to form a colored compound, and similar effects of excess of acid on colorless triphenylmethyl halides or sulfates have frequently been noted.[35] The effect may probably be attributed to hydrogen bonding involving the proton of the acid and the lone pairs of the halide ion.

Triphenylcarbonium ion may also be produced by the action of a very strong acid on triphenylcarbinol, provided that the medium is one of sufficiently low basicity. The carbinol dissolves in concentrated sulfuric acid to give a yellow solution the light absorption of which is identical with that of the chloride in sulfur dioxide,[33] and the molar freezing-point depression of which is four times that produced by a nonelectrolyte.[16a,c] The reaction must be

$$(C_6H_5)_3COH + 2H_2SO_4 \rightleftharpoons (C_6H_5)_3C^+ + OH_3^+ + 2HSO_4^- \qquad (XXI)$$

[35] BAEYER and VILLIGER, *Ber.*, **35**, 1189 (1902). GOMBERG and CONE, *Ann.*, **370**, 142 (1909). MEYER, *Ber.*, **41**, 2568 (1908).

A similar process occurs in formic acid

$$(C_6H_5)_3COH + HCO_2H \rightleftharpoons (C_6H_5)_3C^+ + HCO_2^- + H_2O \quad (XXII)$$
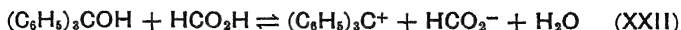
The action of sulfuric or formic acid on the carbinol closely resembles that of $SnCl_4$ on the chloride. The ionization in the first case results from the affinity of the protons of the acid for the hydroxyl ion of the carbinol, in the other from that of the stannic chloride for chloride ion. The carbinol also ionizes, although slowly and incompletely, in sulfur dioxide,[32] the reaction being

$$(C_6H_5)_3COH + SO_2 \rightleftharpoons (C_6H_5)_3C^+ + HSO_3^- \quad (XXIII)$$
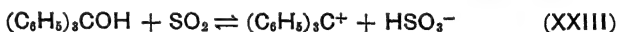
The suggestion has frequently been made that the ionization of the triphenylmethyl halide occurs by way of a displacement of a type important in inorganic complex chemistry.[36]

$$(C_6H_5)_3CCl + H_2O \rightleftharpoons (C_6H_5)_3COH_2^+ + Cl^- \quad (XXIV)$$

In effect, this displacement amounts to a solvation of the carbonium ion instead of the halide ion. The hypothesis is definitely controverted by the isolation and analysis of a number of colored yet anhydrous perchlorates of the type (E)[37]

$$[(C_6H_5)_3C]^+[ClO_4]^-$$
$$(E)$$
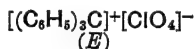
Furthermore, the hypothesis that the colored ion formed by triphenylcarbinol in sulfuric acid has the formula $(C_6H_5)_3COH_2^+$ leads to the incorrect conclusion that the molar freezing-point depression should be twice rather than four times that of a non-electrolyte; the hypothesis that it is $(C_6H_5)_3COSO_3H_2^+$ is also difficult. To judge by the behavior of other alkyl sulfuric acids, which are not measurably basic in sulfuric acid, this should revert to $(C_6H_5)_3COSO_3H$.

Carbonium ions are also formed by the action of sulfuric acid on a restricted number of benzoic acid derivatives.[16g] Unlike benzoic acid, which simply adds a proton according to equation (X), 2,4,6-trimethylbenzoic acid produces a fourfold freezing-point depression by virtue of a reaction that can only be

$$(CH_3)_3C_6H_2COOH + 2H_2SO_4 \rightleftharpoons (CH_3)_3C_6H_2CO^+ + OH_3^+ + 2HSO_4^-$$
$$(XXV)$$
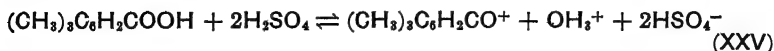
[36] HOFMANN and KIRMREUTHER, *Ber.*, **42**, 4856 (1909). GOMBERG and CONE, *Ann.*, **376**, 183 (1910).

[37] DILTHEY and DINKLAGE, *Ber.*, **62B**, 1834 (1929).

A careful study of the phenomenon has shown that it appears only when two alkyl groups are in the ortho position and that it is assisted by an alkyl group in the para position.[16g]   Consistent with the ease with which hydroxyl ion is removed from these substances by sulfuric acid, their esters are immediately decomposed with removal of CH_3O^- when they are dissolved in sulfuric acid.   Methyl acetate or benzoate is only slowly acted on under the same conditions.

Resonance in the Structure of Ions.—The shifting about of electrons, which can be treated so satisfactorily in terms of the resonance picture, is even more important in the case of ions than it is with electrically neutral substances.   With the exception of simple aliphatic ammonium and alcoholate ions like $CH_3NH_3^+$ and CH_3O^-, the resonance phenomenon determines or greatly modifies the stability of organic ions.   A carboxylate ion is a resonance hybrid of the equivalent structures (F) and (G).

$$\left[R-C \begin{matrix} \ddot{O}\cdot \\ \ddot{O}\cdot \end{matrix} \right]^- \longleftrightarrow \left[R-C \begin{matrix} \ddot{O}\cdot \\ O\cdot \end{matrix} \right]^-$$

$$(F) \qquad\qquad (G)$$

To form the molecular acid by addition of a proton, energy equal to the considerable resonance energy of this symmetrical system must be furnished.   This hinders the process and is chiefly responsible for the fact that formic acid is so much stronger an acid than methyl alcohol.   There is resonance in the acid also

$$R-C \begin{matrix} \ddot{O}\cdot \\ \ddot{O}-H \end{matrix} \longleftrightarrow R-C \begin{matrix} \ddot{O}\cdot \\ O-H \end{matrix}$$

$$(H)$$

but the system is not symmetrical, and the resonance energy is smaller than in the ion.   One might also interpret the situation by noting that the resonance distributes the negative charge of the ion over both oxygen atoms, reducing the density of charge on each and, hence, the intensity of the electrical field that attracts the proton.

In the same way the relatively high acidity of phenols compared with aliphatic alcohols may be attributed to a resonance in the ion

(*I*)

A similar resonance exists in molecular phenol (page 28), but its effect is less because the proton attached to oxygen reduces the number of lone pairs available for the shifts involved in the resonance.

Aniline is stabilized by a resonance

(*J*)
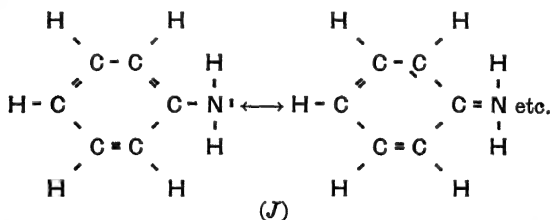
which is impossible in anilinium ion and which, therefore, decreases the basicity of aniline compared with aliphatic amines.

The α-hydrogen atoms of ketones are relatively acidic because the conjugate base (K) is stabilized by a resonance

(*K*)
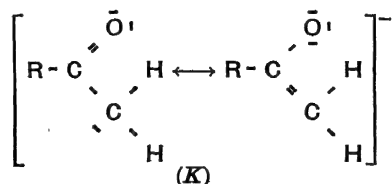
which is closely related to that of the carboxylate ions. A similar resonance exists in the conjugate bases of amides. When two carbonyl groups are present in a suitable position, a larger variety of resonating structures becomes possible and the reso-

(L)
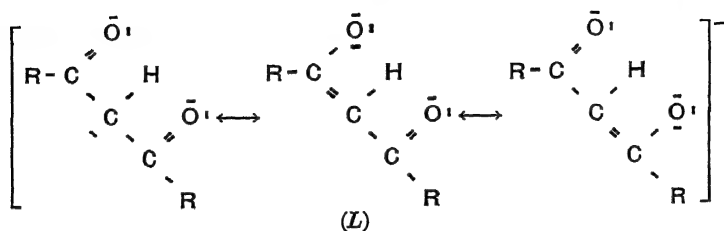
nance energy is greater, the ion more stable, and the ketone more acidic.

(M)
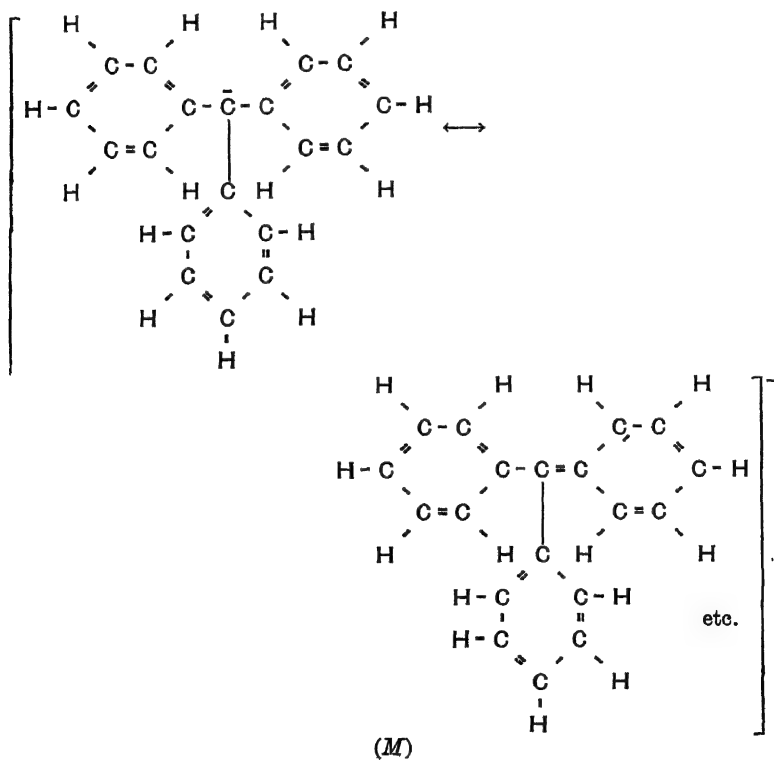
Any other kind of unsaturated group may play the same part as the carbonyl group in the preceding examples, and the acidity of the hydrocarbons listed in Table I may be attributed in every case to a resonance of this sort. In the case of triphenylmethide ion (M) the resonance involves 10 different structures and distributes the charge of the ion over all the ortho and para positions as well as the methane carbon.

The conjugate acids of carbonyl compounds also have hybrid structures

$$\left[\begin{array}{c} \bar{O}\text{-}H \\ R\text{-}C \\ R \end{array} \longleftrightarrow \begin{array}{c} \bar{O}\text{-}H \\ R\text{-}C \\ R \end{array} \right]^{+}$$

$$(N)$$
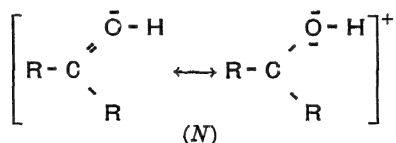
They are neither oxonium ions according to the first structure nor carbonium ions according to the second, but something in between. The conjugate acids of carboxylic acids possess a symmetrical resonance

$$\left[\begin{array}{c} \bar{O}\text{-}H \\ R\text{-}C \\ \bar{O}\text{-}H \end{array} \longleftrightarrow \begin{array}{c} \bar{O}\text{-}H \\ R\text{-}C \\ \bar{O}\text{-}H \end{array} \longleftrightarrow \begin{array}{c} \bar{O}\text{-}H \\ R\text{-}C \\ O\text{-}H \end{array} \right]^{+}$$

$$(O)$$
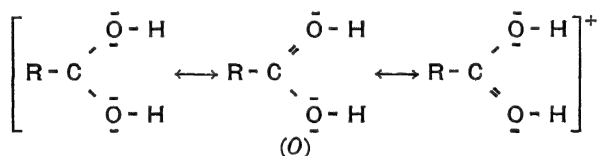
with a large resonance energy. Consequently, benzoic acid is nearly as strong a base as acetophenone (page 271), although in the absence of the resonance the greater positive charge on the oxygen nucleus of the hydroxyl group would be expected to decrease the basicity of the acid. The trimethylbenzoyl ion resonates between doubly and triply bound structures

$$[R\text{-}C = \underset{\sim}{O}\, \cdot \longleftrightarrow R\text{-}C \equiv O\, \cdot]^{+}$$

$$(P)$$
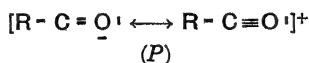
Like the triphenylmethyl radical and the triphenylmethide ion the triphenylcarbonium ion is stabilized by a resonance which this time distributes the positive charge or deficiency of electrons over the ortho and para positions as well as the carbonium carbon.

Light Absorption: Dyestuffs.—Absorption of visible or ultraviolet light by organic compounds is closely linked with unsaturation. Both ethylene and carbonyl compounds absorb in reasonably accessible regions of the spectrum. When two or more unsaturated groups are conjugated, the intensity of the absorption increases, and the region of absorption moves toward longer
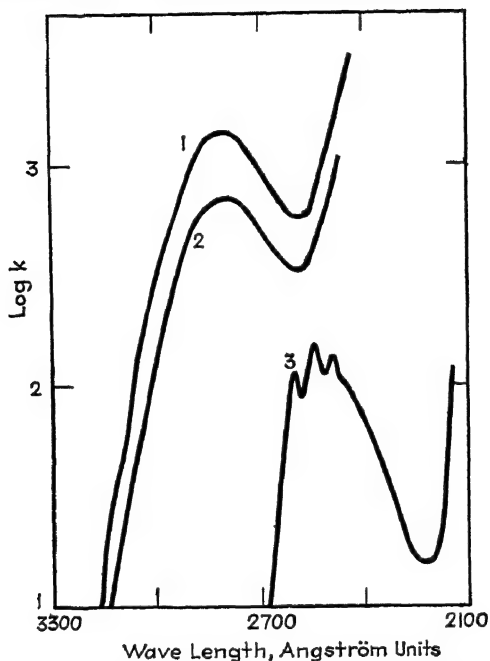
Fig. II-1.—The absorption spectra of (1) aniline, (3) anilinium ion, (2) a mixture of the two.[36]

wave lengths.[38] In terms of the quantum theory the latter effect means that the energy levels of the molecule involved in the light absorption are more closely spaced; the former can be shown to be related to an increased electric moment in some of the resonating structures which may be combined to approximate the wave function of the molecule.[39] In benzene, naphthalene,

[38] SMAKULA, *Angew. Chem.*, **47**, 657 (1934). HAUSER, KUHN, and SMAKULA, *Z. physik. Chem.*, **B29**, 363; 371; 378; 384; 391; 417 (1935). PIPER and BRODE, *J. Am. Chem. Soc.*, **57**, 135 (1935).

[39] PAULING in GILMAN, "Organic Chemistry," New York, 1938, p. 1888.

and the like, the absorption becomes much more intense and moves to a region not far out of the visible region. In many benzene derivatives, it moves still farther into the visible region, and the substance becomes colored.

The electronic systems of such substances are considerably distorted by the formation or rupture of a valence bond, and this results in changes in light absorption. Figure 1 shows in curve 1 the absorption spectrum of molecular aniline, in curve 3 that of anilinium ion (curve 2 is the absorption of aniline in a solution in which it is partly ionized). If human eyes were sensitive in the region of 3000A, aniline would be a useful acid-base indicator.

It need therefore occasion no surprise that the conversion of triphenylcarbinol, which absorbs strongly in the near ultraviolet, to triphenylcarbonium ion should produce a substance the intense yellow color of which indicates that it absorbs strongly in the violet end of the visible spectrum. The direction of the shift in wave length is indeed the expected one. Any change that increases the volume accessible to the unsaturation electrons produces a shift to longer wave lengths.[39]

The name *halochromie* was applied to the reversible conversion of a colorless to a highly colored compound by strong acid at a time when the nature of the reaction involved was not understood. The typical halochromic compounds are the triphenylcarbinols and substances of the type of benzalacetophenone, but the definition would cover a great many simple oxygen bases the conjugate acids of which are strongly colored, such as anthraquinone and benzoylnaphthalene (page 266). Benzalacetophenone itself gives a twofold freezing-point depression in sulfuric acid; hence, the colored substance is simply its conjugate acid[16e]

(Q)
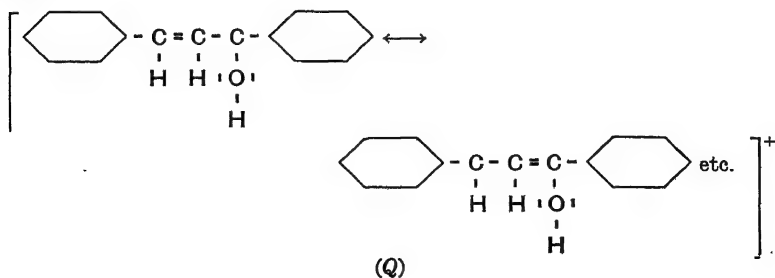
The resonance also involves the benzene rings and includes a structure with a carbon-oxygen double bond.   Dibenzalacetone and cinnamylacetophenone give fourfold depressions and ionize in a more complicated fashion to yield, likewise, highly colored products.

Benzalacetophenone and similar substances form addition compounds with stannic chloride of the type (R) which are identical in color with the conjugate acids of the ketones.[40]   The

$$
\begin{array}{ccc}
C_6H_5 & & C_6H_5 \\
| & & | \\
CH & & CH \\
\| & & \| \\
CH \ \ \cdot Cl\cdot & \cdot Cl\cdot & CH \\
| & & | \\
C - O - & Sn & - O - C \\
| & & | \\
C_6H_5 \cdot Cl\cdot & \cdot Cl\cdot & C_6H_5
\end{array}
$$

(R)
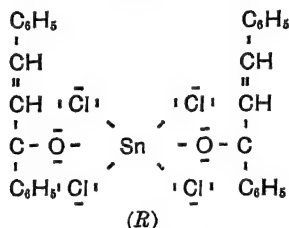
ability of the tin atom in stannic chloride to attain its full shell of 12 valence electrons by attaching itself to the lone pairs of oxygen compounds frequently lends this substance properties that closely resemble those of a strong acid.[41]   The same thing is true in even higher degree of $AlCl_3$ and BF_3, both of which tend strongly to attain a filled shell of eight electrons for the metal atom.

The triphenylmethane dyestuffs are triphenylcarbonium compounds that have been stabilized by the presence of NH_2, $N(CH_3)_2$, OH, or similar groups in the para positions of at least two of the rings.   The symmetry of the resulting resonance between the structures (S) so stabilizes the ion that it is formed from the carbinol by the action of weak acids in aqueous solution. At the same time the stabilization renders it more difficult to add a proton to nitrogen, so that the range of acidity over which this ion is stable is relatively large.[42]   The light absorption in the symmetrical system moves toward longer wave lengths yielding green, blue, and violet dyes.   The carbinol is colorless, and the doubly positive and unsymmetrical ion obtained by adding a

[40] PFEIFFER, "Organische Molekülverbindungen," Stuttgart, 1927.

[41] LEWIS, *J. Franklin Inst.*, **226**, 293 (1938).

[42] SCHWARZENBACH, BRANDENBURGER, OTT, and HAGGER, *Helv. Chim. Acta*, **20**, 490 (1937).   SCHWARZENBACH and OTT, *ibid.*, **20**, 627 (1937).

proton to one of the nitrogens in (*S*) has the yellow color of
triphenylcarbonium ion.   Many other problems in color and
constitution may probably be clarified by the same kind of
reasoning as that which Schwarzenbach has so successfully

```
                    H - N - H
                        ‖
              H         C         H
                ╲     ╱   ╲     ╱
                  C       C
                  ‖       ‖
                  C       C
                ╱   ╲   ╱   ╲
              H       C       H
                      ‖
    H         H       H       H         H
      ╲     ╱           ╲     ╱
        C - C             C - C       H
      ╱       ╲         ╱       ╲   ╱
  H - C         C ━━━━ C         C - N ⟵⟶
      ╲       ╱         ╲       ╱   ╲
        C ═ C             C ═ C       H
      ╱       ╲         ╱       ╲
    H           H     H           H

              (S)
                              H - N̄ - H

                          H       C       H
                            ╲   ╱   ╲   ╱
                              C       C
                              ‖
                              C       C
                            ╱   ╲   ╱   ╲
                          H       C       H
                                  ‖
              H       H           H       H
                ╲   ╱               ╲   ╱
                  C - C               C ═ C       H
                ╱       ╲           ╱       ╲   ╱
            H - C         C ━━━━ C         C ═ N
                ╲       ╱           ╲       ╱   ╲
                  C ═ C               C ═ C       H
                ╱       ╲           ╱       ╲
              H           H       H           H
```
[ ] +
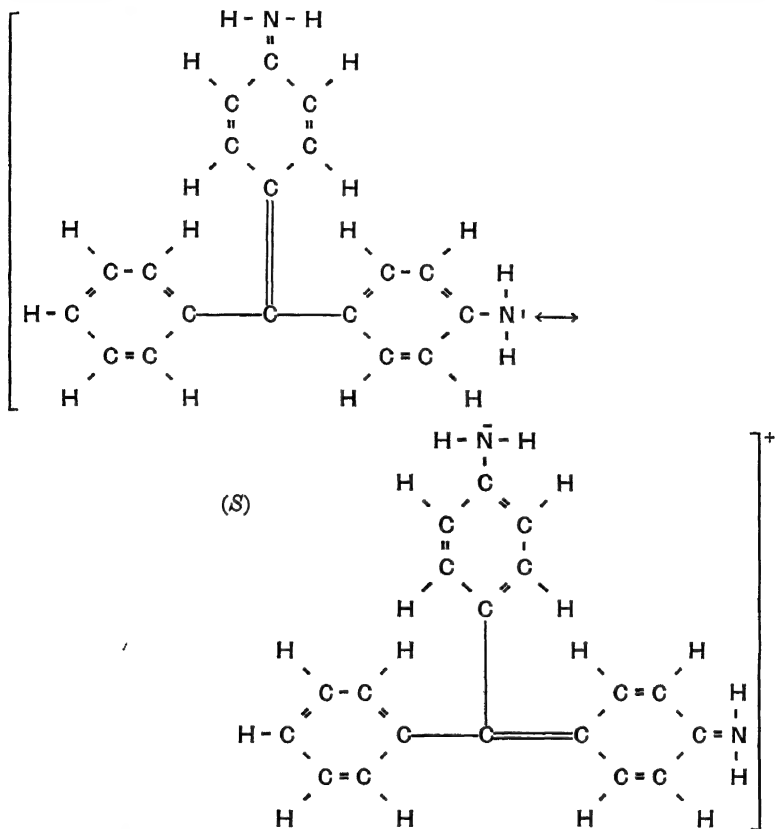
employed with the triphenylmethane dyes.   Much in the way
of data and empirical generalization in this field is already
available.[43]

**Localization and Distribution of Charge: Dipolar or Zwitter
Ions.**—When only saturated structures are involved, the charge
on an ion may fairly well be represented as localized on a partic-

[43] DILTHEY and WIZINGER, *J. prakt. Chem.*, **118**, 321 (1928). BURAWOY,
Ber., **63B**, 3155 (1930); **64B**, 462 (1931).

ular atom.   A formal charge may be calculated for each atom in the molecule by algebraic addition of the positive charge on its nucleus with one unit of negative charge for each unshared electron and one-half unit for each shared electron assignable to the atom in question.[44]   This charge usually vanishes for each of the atoms in a neutral molecule and for all but one of the atoms in a singly charged ion.   Thus the nitrogen atom in ammonia has a nuclear charge of $+7$, it possesses two wholly owned $1s$ electrons, two wholly owned electrons in the lone pair, and a half share in each of the six electrons that bond the three hydrogens.   The formal charge is, therefore,

$$+7 - 2 - 2 - \tfrac{1}{2} \cdot 6 = 0.$$

In ammonium ion the lone pair has become a shared pair, and the formal charge is $+7 - 2 - \tfrac{1}{2} \cdot 8 = +1$.

In unsaturated substances the formal charge is the weighted mean of the charges that the atom possesses in the various resonating structures.   Thus in CH_3^+ the formal charge on carbon is $+1$; in triphenylcarbonium ion the charge on the methyl carbon is less than 1 because of the participation of resonance structures in which the charge is on the ortho and para carbon atoms.

In special cases an extremely uneven distribution of charge may exist in a neutral molecule.   Thus the aliphatic amino acids exist chiefly in the form (T) rather than the form (U) which differs in the position of one hydrogen.   In (T) the formal
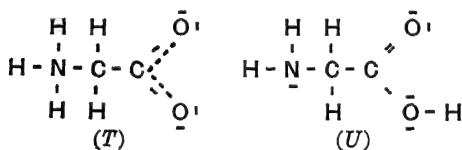
charge on nitrogen is $+1$, that on each of the oxygens is $\tfrac{1}{2}$; in (U) it is zero on all atoms.   Molecules with charge distributions like that of (T) are called *dipolar ions* or *Zwitterionen.*[45]   The evidence that they represent the predominant form of the ali-

[44] PAULING in GILMAN, "Organic Chemistry," New York, 1938, p. 1864.
[45] BREDIG, *Z. physik. Chem.*, **13**, 323 (1894).   KÜSTER, *Z. anorg. allgem. Chem.*, **13**, 136 (1897).

phatic amino acids is as follows. The amino acids are, in the first place, much too weak to fit structure (U). The pK_a for glycine is 9.75, compared with 4.75 for acetic acid. The acid strength is however reasonable for structure (T).[46] Further, the formaldehyde derivatives (V) have the strengths of ordinary

$$H_2C = \bar{N} - CH_2 - COOH$$
$$(V)$$
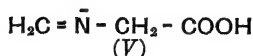
carboxylic acids.[46] Similar evidence is derived from the comparison of the base strengths of amino acids with those of their esters.[47] The very high dielectric constant of aqueous solutions of the amino acids is consistent with the large dipole moment that structure (T) must possess,[48] and the similarity of the Raman spectrum to that of carboxylate ions and the absence of the lines characteristic of the COOH and of the NH_2 groups offer further evidence.[49]

Aminobenzoic acids, unlike the aliphatic compounds, exist mostly in a form analogous to (U), but sulfanilic acid and the like are present predominantly in the dipolar ion form.[46,48]

Carbonium Ions and Carbanions as Reaction Intermediates.— Although the existence of carbonium ions and carbanions can be directly demonstrated only in those cases where they are so stabilized by resonance that their concentration becomes large, there is no reason to doubt their presence in smaller concentrations in other cases. Indeed the phrase "stabilized by resonance" implies their existence in the absence of the resonance and a continuous increase in concentration as the extent of the stabilization increases. In particular, they may very probably appear as transient intermediates in the course of reactions that lead from nonionic reactants to nonionic products. The recognition of this possibility[50] has played an important part in the

[46] BJERRUM, *Z. physik. Chem.*, **104**, 147 (1923).

[47] EBERT, *Z. physik. Chem.*, **121**, 385 (1926). EDSALL and BLANCHARD, *J. Am. Chem. Soc.*, **55**, 2337 (1933).

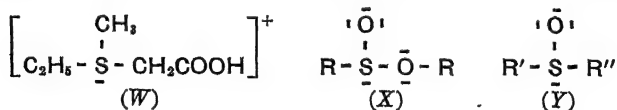[48] HEDESTRAND, *Z. physik*, **135**, 36 (1928).

[49] EDSALL, *J. Chem. Phys.*, **4**, 1 (1936); **5**, 225 (1937).

[50] MEERWEIN and VAN EMSTER, *Ber.*, **55**, 2500 (1922). HANHART and INGOLD, *J. Chem. Soc.*, 997 (1927). WARD, *ibid.*, 2285 (1927). WHITMORE, *J. Am. Chem. Soc.*, **54**, 3274 (1932). ARNDT and EISTERT, *Ber.*, **69B**, 2381 (1936). HAUSER and RENFROW, *J. Am. Chem. Soc.*, **59**, 1823 (1937).

recent rapid development of the understanding of reaction mechanisms in organic chemistry.

Configuration of Tercovalent Carbon.—When four different groups are attached to one carbon atom, the molecule is (unless there is internal compensation as in mesotartaric acid) devoid of center and planes of symmetry. Consequently, the substance concerned is capable of existence in optically active forms. If one of the groups is removed, three situations may arise. (1) The remaining three groups may retain essentially their original configuration, in which case the ion or radical thus formed will be capable of optical activity. If this is so, the product formed from an active reactant by way of the ion or radical will be active. (2) The ion or radical may settle down into a form in which the three groups and the central carbon atom lie in a plane. Since this is a plane of symmetry, there is no possibility of activity. (3) Finally, the asymmetric form may be stable, but the energy of activation required to convert one enantiomorph into the other may be so small that the molecule oscillates rapidly between dextro and levo forms. In this case optical activity is possible in principle, but racemization is so rapid that the active forms cannot be isolated. The reaction product produced by way of such an intermediate from an active reactant will be racemized to an extent that depends upon the relative rates of the conversion of the intermediate to its enantiomorph and to nonracemizing products.

There is little basis, either theoretical or experimental, on which to choose among these alternatives when the central atom is carbon, but two of them are clearly recognizable with other elements. The first case appears with the optically active sulfonium ions in which sulfur is linked to three different groups as in (W).[51] These ions are certainly present in the conducting

$$\left[\begin{array}{c} CH_3 \\ | \\ C_2H_5 - S - CH_2COOH \end{array}\right]^+ \qquad \overset{..}{\underset{..}{O}} \\ R - \overset{|}{\underset{..}{S}} - \overset{..}{\underset{..}{O}} - R \qquad \overset{..}{\underset{..}{O}} \\ R' - \overset{|}{\underset{..}{S}} - R''$$
$$(W) \qquad\qquad\qquad (X) \qquad\qquad (Y)$$

solutions of the sulfonium halides, and it is difficult to see how the ion could form a valence link to halide ion under any con-

[51] POPE and PEACHEY, *J. Chem. Soc.*, **77**, 1072 (1900). SMILES, *ibid.*, **77**, 1174 (1900).

ditions. A similar configuration appears in the likewise active sulfinic esters (X) and sulfoxides (Y).[52]

The third alternative, that of rapid racemization, is represented by tercovalent nitrogen compounds. The pyramidal structure of ammonia (pages 15, 33), if it is also present in amines, should lead to activity when three different groups are attached to nitrogen. Nevertheless, no optically active substance the activity of which rests unambiguously upon this kind of structure has been obtained in spite of much investigation.

Both amines and the active sulfur compounds carry a lone pair on the asymmetric atom and are therefore analogous to a carbanion. One might therefore expect the possibility of rapidly racemizing active forms of carbanions. It must be remembered, however, that the pyramidal form cannot be much more stable than a planar form in which the wave functions of the two unshared electrons lie symmetrically above and below the plane of the nuclei in the same way as does that of the odd electron in the methyl radical (page 16).

A stable asymmetric structure has been suggested for tercovalent carbon in the anion that is the conjugate base of an aliphatic nitrocompound.[53] The usually accepted structure may be interpreted as the hybrid (Z).

(Z)
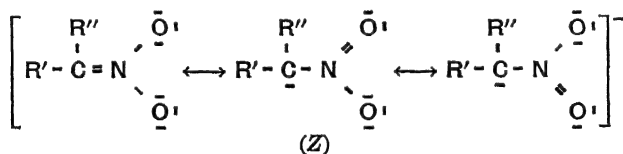
The relatively high acidity of the nitrocompound must be attributed to the predominance of the first of these structures in

(AA)
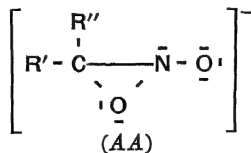
[52] PHILLIPS, *J. Chem. Soc.*, **127**, 2552 (1925); HARRISON, PHILLIPS, and KENYON, *ibid.*, 2079 (1926).

[53] KUHN and ALBRECHT, *Ber.*, **60**, 1297 (1927). SHRINER and YOUNG, *J. Am. Chem. Soc.*, **52**, 3332 (1930).

the ion, because only in this is the electron pair that links the hydrogen otherwise involved in the ion. Since this structure possesses a plane of symmetry, the optical activity of the ion is not accounted for. The structure (AA), which has also been proposed for these ions,[54] would, however, be asymmetric.

One other case in which a stable optically active carbanion is formed has been reported.[55] On the other hand, there is much kinetic evidence (page 98) that the products formed from active reactants by way of carbanions are completely racemic.

There is no evidence for the stable existence of optically active radicals or carbonium ions. The negative evidence is not entirely convincing, for the only compounds that can be isolated are stabilized by resonance (pages 30, 59) in a way, involving double bonding of the asymmetric carbon, that must strongly favor a planar and inactive configuration. The possibility of active carbonium ions as unstable intermediates is an involved question (Chap. VI).

[54] HOLLEMAN, *Rec. trav. chim.*, **13**, 405 (1894).
[55] WALLIS and ADAMS, *J. Am. Chem. Soc.*, **55**, 3838 (1933)

CHAPTER III

EQUILIBRIUM AND ENERGY OF REACTION

The Boltzmann Principle.—The fundamental principle that describes the behavior of chemical and physical systems at equilibrium is the Boltzmann expression[1]

$$N = Ap e^{-\epsilon/kT} \tag{1}$$

N is the number of molecules present at equilibrium in a state in which the energy per molecule is ϵ; A is a proportionality constant; p, the *a priori probability*, is a factor that expresses the number of fundamentally different ways in which the energy ϵ can be attained; k is the Boltzmann constant defined by

$$k = \frac{R}{N} \tag{2}$$

and T is the absolute temperature. The principle may be derived from more abstract considerations of probabilities, but the justification for these as for the Boltzmann expression itself is the widespread applicability of the expression.

The Barometric Formula.—A familiar example of the Boltzmann principle is the way in which the molecules of the earth's atmosphere distribute themselves in its gravitational field. The energy is given by

$$\epsilon = mgh \tag{3}$$

where m is the mass of the molecule, g the gravitational constant, and h the height above some arbitrary "sea level" at which the energy is taken to be zero. The factor p is unity; hence,

$$N = A e^{-mgh/kT} \tag{4}$$

---

[1] Standard texts on statistical mechanics are Fowler, "Statistical Mechanics," Cambridge, 1936, and Tolman, "The Principles of Statistical Mechanics," Oxford, 1938. An elementary treatment is given in Ubbelohde, "Modern Thermodynamical Principles," Oxford, 1937.

The number of molecules may be replaced by the pressure P, which is proportional to it; the ratio m/k may be converted to M/R, where M is the molecular weight, by multiplying both numerator and denominator by N; and the constant A evaluated as the pressure P_0 at sea level by substituting $h = 0$ and $P = P_0$ in equation (4). The result

$$P = P_0 e^{-Mgh/RT} \tag{5}$$

is the usual form of the barometric formula, a familiar, exact, and useful equation.
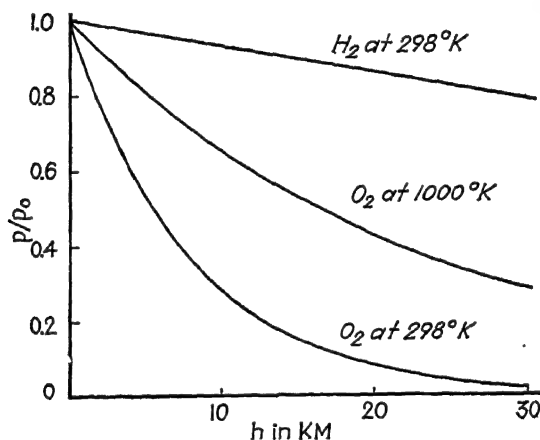
Fig. III-1.—The Boltzmann principle: variation of gas pressure with height in a gravitational field.

Figure 1 shows how the pressure varies with the height, approaching but never attaining zero. The rate of decrease is greater, the lower the temperature and the greater the molecular weight. The same equation applies to the distribution of colloidal molecules in a supercentrifuge except that a much larger centrifugal acceleration replaces g. A similar expression describes the distribution of ions in an electrical field and is at the basis of all modern theories of the properties of electrolytes.

The Maxwell Distribution of Translational Velocities.— Because of its motion through space, a molecule in a gas possesses an energy

$$\epsilon = \frac{1}{2}mv^2 \tag{6}$$

in which v is the velocity. Since any given velocity and energy may be attained by a variety of directions of motion, the factor p of equation (1) may no longer be set equal to unity but may be shown to have a value proportional to v^2. The value of A may be derived from the fact that the total number of molecules must equal the sum of the numbers having the various velocities. The complete Maxwell equation is

$$dN = 4\pi N\left(\frac{m}{2\pi kT}\right)^{3/2} v^2 e^{-mv^2/2kT} dv \tag{7}$$

in which dN is the number of molecules the velocities of which lie between v and $v + dv$. Because of the v^2 factor this expression has a zero value when $v = 0$ and first rises and then falls with increasing v. The equation has been amply verified both by direct measurement of the velocities and through a wide variety of corollaries.[2]

Internal Kinetic Energy: Quantization.—Aside from the translational energy of its motion through space, a molecule possesses internal energy due to its electronic system, to the rotational motion of the molecule about its center of gravity, and to the motions of the atoms with respect to each other within the molecule. Unlike translational motion, the energy of which is continuously variable [hence the differentials in equation (7)], the internal energy may possess only certain sharply defined values (page 3) and is said to be *quantized*. The permitted values of the energy may be determined from the study of the spectrum and in certain cases may be derived from the Schrödinger equation (page 5). Thus the energy of vibration of two atoms in a diatomic molecule takes values that, to a good approximation, are represented by the equation

$$\epsilon = \left(v + \frac{1}{2}\right)\epsilon_0 \tag{8}$$

in which v, the vibrational quantum number, may be any integer and ϵ_0 is a constant the value of which is determined by the masses of the vibrating particles and the force law operating between them. Its value is greater, the lighter the particles and the

[2] Discussed by Herzfeld and Smallwood in Taylor, "Treatise on Physical Chemistry," p. 110, New York, 1931.

more stiffly they are bound together. This equation permits the
vibrational energy to have only the values $\frac{1}{2}\epsilon_0$, $\frac{3}{2}\epsilon_0$, $\frac{5}{2}\epsilon_0$, etc.
By the Boltzmann principle the numbers of molecules having
each of these amounts of energy will be proportional to the
quantities

$$e^{-\frac{1}{2}\epsilon_0/kT} \qquad e^{-\frac{3}{2}\epsilon_0/kT} \qquad e^{-\frac{5}{2}\epsilon_0/kT}, \text{ etc.}$$

respectively. The proportionality constant may be obtained by
noting that the total number of molecules N must equal the
sum of the numbers in the various energy states

$$N = \sum^{v} A e^{-(v + \frac{1}{2})\epsilon_0/kT} = A \sum^{v} e^{-(v + \frac{1}{2})\epsilon_0/kT} \tag{9}$$

Hence the fraction N_v/N in the state of quantum number v is

$$N_v/N = \frac{e^{-(v + \frac{1}{2})\epsilon_0/kT}}{\Sigma e^{-(v + \frac{1}{2})\epsilon_0/kT}} \tag{10}$$

It is a characteristic and important consequence of the exponen-
tial form of this equation that there is a temperature below
which practically all the molecules are in the state of lowest
energy, $\frac{1}{2}\epsilon_0$. This is shown in Table I in which the fraction of
molecules in various levels at various temperatures is calculated
for a value of ϵ_0 of 5.52×10^{-14} erg.

TABLE I

Temp., K	Fraction of molecules in state for which v equals				
	0	1	2	3	4
400	0.632	0.232	0.086	0.020	0.007
200	0.865	0.117	0.016	0.002	0.000
133	0.949	0.049	0.002	0.000	0.000
100	0.981	0.018	0.000	0.000	0.000
80	0.993	0.007	0.000	0.000	0.000

When the temperature is so low that practically all the mole-
cules are in the state of lowest vibrational energy, the vibrational
energy is said to be *frozen out*. Freezing out occurs with any
quantized energy, the temperature required depending upon the
form of the equation which determines the permitted energies of

the system. The more closely spaced the energy levels [*e.g.*, the smaller the value of ϵ_0 in equation (8)], the lower the temperature necessary to freeze out the energy in question.

Equilibrium in an Isomeric Change.—The Boltzmann principle also determines the equilibrium in a chemical reaction such as the conversion of the ketonic form of acetacetic ester to the enolic form. When the symbols K and E are used for the two forms, the condition for equilibrium is

$$\frac{[E]}{[K]} = K \tag{11}$$

If the temperature is so low that the internal vibrational and rotational energies of the two molecules are frozen out, all the molecules of the keto form are in the same state of energy ϵ_K, and all the enol molecules have the energy ϵ_E. According to the Boltzmann equation the number of enol molecules is given by

$$N_E = A e^{-\epsilon_E/kT} \tag{12}$$

and the number of keto molecules by

$$N_K = A e^{-\epsilon_K/kT} \tag{13}$$

By dividing one equation by the other,

$$\frac{N_E}{N_K} = e^{-(\epsilon_E - \epsilon_K)/kT} \tag{14}$$

Since ϵ/k may be replaced by E/R with E the energy per mole and since the ratio of the numbers of molecules of the two kinds is equal to the ratio of their concentrations, *i.e.*, to the equilibrium constant K, equation (14) reduces to

or
$$\left.\begin{array}{l} K = e^{-\Delta E_0/RT} \\[2mm] \Delta E_0 = -RT \ln K \end{array}\right\} \tag{15}$$

in which ΔE_0 is the energy per mole of enol form minus that of keto form. Since volume changes are not involved, ΔE_0 is practically identical with the heat of reaction at constant pressure ΔH.

Unfortunately, this simple equation is not in general applicable to systems at ordinary temperatures because the vibrational and

rotational energies are not frozen out.   Consequently, the enol molecules exist in a variety of states ϵ_0^E, ϵ_1^E, ϵ_2^E, etc., and the number of molecules in each of these is

$$A p_0^E e^{-\epsilon_0 E/kT}, \qquad A p_1^E e^{-\epsilon_1 E/kT}, \qquad A p_2^E e^{-\epsilon_2 E/kT}, \text{ etc.}$$

The total number of enol molecules is the sum of all these terms, and the total number of keto molecules is the sum of a similar series involving the various energies that a keto molecule may possess.   Dividing one of these by the other gives the equilibrium constant K in the form

$$K = \frac{p_0^E e^{-\epsilon_0 E/kT} + p_1^E e^{-\epsilon_1 E/kT} + p_2^E e^{-\epsilon_2 E/kT} + \cdots}{p_0^K e^{-\epsilon_0 K/kT} + p_1^K e^{-\epsilon_1 K/kT} + p_2^K e^{-\epsilon_2 K/kT} + \cdots} \quad (16)$$

a much more difficult expression than equation (15).   It may be formally simplified in a way that points up the problem involved by defining a *partition function* f_E of the enol form by the equation

$$f_E = p_0^E + p_1^E e^{-(\epsilon_1 E - \epsilon_0 E)/kT} + p_2^E e^{-(\epsilon_2 E - \epsilon_0 E)/kT} + \cdots \quad (17)$$

and a partition function f_K for the keto form by a similar equation.   Since

$$\frac{e^{-\epsilon_0 E/kT}}{e^{-\epsilon_0 K/kT}} = e^{-\Delta E_0/RT} \quad (18)$$

where ΔE_0 has the same meaning as in equation (15), *i.e.*, the energy of reaction per mole at temperatures so low that vibrational and rotational energies are frozen out, equation (16) can be put in the form

$$\left. \begin{array}{l} K = \dfrac{f_E}{f_K} e^{-\Delta E_0/RT} \\[2mm] \quad \\[2mm] \Delta G^0 = -RT \ln K = \Delta E_0 - RT \ln\left(\dfrac{f_E}{f_K}\right) \end{array} \right\} \quad (19)$$

or

ΔG^0 is the standard free-energy change of the reaction, the ΔF^0 of the symbolism used by G. N. Lewis.[3]

An expression for the heat of reaction may be derived from the following considerations: Differentiation of the definition of the partition function (17) leads to

[3] LEWIS and RANDALL, "Thermodynamics," New York, 1923.

$$\frac{df}{dT} = \frac{p_1(\epsilon_1 - \epsilon_0)}{kT^2}e^{-(\epsilon_1 - \epsilon_0)/kT} + \frac{p_2(\epsilon_2 - \epsilon_0)}{kT^2}e^{-(\epsilon_2 - \epsilon_0)/kT} + \cdots \quad (20)$$

On multiplication by kT^2/f, this leads, in view of $df/f = d\ln f$, to

$$kT^2\frac{d\ln f}{dT} = (\epsilon_1 - \epsilon_0)\frac{p_1 e^{-(\epsilon_1 - \epsilon_0)/kT}}{\sum_i p_i e^{-(\epsilon_i - \epsilon_0)/kT}} +$$

$$(\epsilon_2 - \epsilon_0)\frac{p_2 e^{-(\epsilon_2 - \epsilon_0)/kT}}{\sum_i p_i e^{-(\epsilon_i - \epsilon_0)/kT}} + \cdots \quad (21)$$

Each term on the right of this equation is the product of a quantity $\epsilon_1 - \epsilon_0$, $\epsilon_2 - \epsilon_0$, etc., which is the excess of energy of a molecule in a given state over that in the state of lowest energy, by a Boltzmann factor which gives the fraction of the molecules in that state. The sum on the right is therefore the average excess energy of all the molecules. If both sides of the equation are multiplied by N, the right side becomes the excess energy per mole over the energy in the lowest state. Hence,

$$RT^2\frac{d\ln f}{dT} = E - E_0 \quad (22)$$

Differentiation of equation (19) and insertion of the values of $d\ln f/dT$ from equation (22) lead to

$$RT^2\frac{d\ln K}{dT} = \Delta E_0 + (E^B - E_0^B) - (E^K - E_0^K) \quad (23)$$

and

$$RT^2\frac{d\ln K}{dT} = E^B - E^K \quad (24)$$

Since volume changes are not involved, the difference $E^B - E^K$ is identical with the heat of reaction ΔH. The statistical treatment is therefore consistent with the well-known thermodynamic formula

$$\Delta H = RT^2\frac{d\ln K}{dT} \quad (25)$$

From equations (22), (23), and (25), it follows that

$$\Delta H = \Delta E_0 + RT^2\frac{d\ln (f_B/f_K)}{dT} \quad (26)$$

Equations (19) and (26) are the foundations of all theoretical studies of chemical equilibrium. They have been amply veri-

fied by studies on reactions involving only those simple molecules for which the energy levels necessary for the calculation of the partition functions may be determined spectroscopically.[4] Their utility is brilliantly confirmed by their function as the basis of all modern investigations on isotope separation.[5]　In the form of the third law of thermodynamics,[3] they have been verified in a large variety of other cases in terms of the following considerations: By a well-known thermodynamic formula

$$\frac{d\Delta H}{dT} = \Delta C_P \qquad (27)$$

where ΔC_P is the difference in heat capacities of products and reactants, it follows that

$$\Delta H - \Delta E_0 = \int_0^T \Delta C_P dT \qquad (28)$$

because the heat of reaction must necessarily approach ΔE_0 when, by the approach of the temperature to the absolute zero, the vibrational and rotational energies become frozen out.　By comparison with equation (26), it follows that

$$RT^2 \frac{d \ln (f_E/f_K)}{dT} = \int_0^T \Delta C_P dT \qquad (29)$$

From this equation and the knowledge that the f's approach unity at low temperatures, it is possible to calculate the quantity f_E/f_K from measurements of the specific heat of reactants and products over the range of temperature from absolute zero to the temperature of reaction.

Potential Energies and Kinetic Energies in Reacting Systems. Because of the presence in equations (19) and (26) of terms involving the partition functions and because these involve the kinetic energies of vibration and rotation, any approach to the effect of structure upon equilibrium or heat of reaction that treats a molecule as a rigid lifeless structure can be no more than the crudest approximation.　The liveliness, the flexibility that is characteristic of a complicated organic molecule, is not lost even at the absolute zero; for it is an amply verified conclusion

[4] GIAUQUE, *J. Am. Chem. Soc.*, **52**, 4816 (1930).

[5] *E.g.*, UREY and GREIFF, *J. Am. Chem. Soc.*, **57**, 321 (1935).

of the quantum theory that the lowest energy state of a vibrating system is not a state in which there is no energy of vibration. In the case represented by equation (8) the smallest value that the quantum number v may have is zero, since the energy cannot be negative. But when $v = 0$, the vibrating system still possesses the energy $\frac{1}{2}\epsilon_0$, which is called its *zero-point energy*. Consequently the E_0 of equations (19) and (26) involves kinetic as well as potential energies, and the equations may profitably be expanded to

$$\Delta G^\circ = -RT \ln K = \Delta E_P + \Delta E_z - RT \ln \left(\frac{f_E}{f_K}\right) \quad (30)$$

$$\Delta H = \Delta E_P + \Delta E_z + RT^2 \frac{\mathrm{d} \ln (f_E/f_K)}{\mathrm{d}T} \quad (31)$$

Here ΔE_P is the difference in potential energy per mole between reactants and products and ΔE_z the difference in zero-point energy.

Any consideration of equilibrium or of heat of reaction must therefore involve two different effects. The term ΔE_P in equations (30) and (31) is the energy change that would accompany the reaction if both reactants and products could be completely deprived of their energy of motion. This is the quantity in terms of which such concepts as energy of linkage, resonance energy, electron displacements, and dipole fields must be discussed. But neither equilibrium constant nor heat of reaction is in general determined by ΔE_P alone, the quantity ΔE_z and the terms involving the partition functions are of coordinate importance, and these involve a knowledge of the kinds of vibrational and rotational motion that the molecule can execute.

There are two possible experimental approaches to the determination of the zero-point energy and the partition function of a molecule. In simple cases the energy levels may be determined spectroscopically; in general, heat-capacity measurements at low temperatures may be applied (page 76). In most cases data are unavailable at present for either approach.

It is important to avoid confusion of these statistical and structural considerations with those derived from the thermodynamic formula

$$\Delta G^\circ = \Delta H - T\Delta S^\circ \quad (32)$$

which may be taken as a definition of the entropy S. Formally, this equation represents the free-energy change as the difference between two quantities, the heat of reaction ΔH and the temperature entropy product $T\Delta S^\circ$, but the separation is of no assistance in the problem of structure and reactivity because ΔH depends upon both kinetic and potential energies and is likely to differ from ΔE_P quite as much as ΔG° does.

Fortunately, there is an experimentally recognizable special case in which the effect of the kinetic energies is negligible. If

$$\Delta G^\circ = -RT \ln K = \Delta H \qquad (33)$$

and therefore

$$\Delta S^\circ = 0 \qquad (34)$$

it is a necessary result of equations (30) and (31) that both $\ln (f_E/f_X)$ and $[d \ln (f_E/f_X)]/dT$ are zero and consequently that f_E/f_X is equal to 1 and remains 1 at all temperatures. This can be true only if the energy-level spacings of reactants and products are identical, which implies that their zero-point energies are also equal and that $\Delta E_z = 0$. If therefore equation (33) or (34) is satisfied experimentally, it follows that

$$\Delta E_P = \Delta H = \Delta G^\circ = -RT \ln K \qquad (35)$$

and either $-RT \ln K$ or ΔH may be taken as a measure of the difference in potential energy between reactants and products. The condition of equation (33) or (34) can be satisfied only in reactions in which there is no change in the number of molecules; otherwise, the kinetic energy of translation complicates the situation. Most problems in structural organic chemistry may, however, be reduced to the study of reactions of this type.

An Example of Equilibrium in a Nonionic System.—The addition of bromine to phenanthrene[6]

$$C_{14}H_{10} + Br_2 \rightleftharpoons C_{14}H_{10}Br_2 \qquad (I)$$
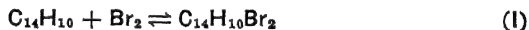
involves a change in the number of molecules; the reaction

$$C_{14}H_{10}Br_2 + XC_{14}H_9 \rightleftharpoons C_{14}H_{10} + XC_{14}H_9Br_2 \qquad (II)$$
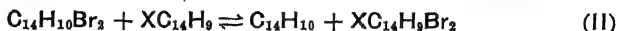
does not. Yet the problem of the effect of the substituent X upon the equilibrium of the bromine addition reduces to that of the equilibrium in reaction (II). The equilibrium constant

[6] Fieser and Price, *J. Am. Chem. Soc.*, **58**, 1838 (1936).

of reaction (II) is the ratio of the equilibrium constants of reaction (I) and of the reaction

$$XC_{14}H_9 + Br_2 \rightleftharpoons XC_{14}H_9Br_2 \tag{III}$$

i.e.,

$$K_{II} = \frac{K_{III}}{K_I} \tag{36}$$

Further, the values of such thermodynamic quantities as ΔH, $\Delta G°$, and $\Delta S°$ for reaction (II) are the differences in the corresponding quantities for reactions (I) and (III), *e.g.*,

$$\Delta H_{II} = \Delta H_{III} - \Delta H_I \tag{37}$$

TABLE II.—THERMODYNAMIC DATA FOR THE PHENANTHRENE-BROMINE REACTION AT 25°C[6]

X	K	$\Delta G°$	ΔH	$\Delta S°$
2-CO$_2$H.....................	0.730	+187	— 3380	— 12
3-CO$_2$H.....................	0.404	+538	— 190	— 2
2-CO$_2$CH$_3$..................	0.726	+190	— 4870	— 16
3-CO$_2$CH$_3$..................	0.561	+343	— 4800	— 17
2-Cl.........................	0.691	+220	—10,630	— 36
3-Cl.........................	0.739	+179	— 8170	— 28
2-Br.........................	0.661	+246	— 8400	— 29
3-Br.........................	0.661	+246	— 5830	— 20
2-*t*-C$_4$H$_9$..................	1.39	—196	+ 4270	+ 15
3-*t*-C$_4$H$_9$..................	2.03	—420	— 5240	— 19

Probable error in $\Delta S°$ 5 cal./deg.

Values of K, $\Delta G°$, ΔH, and $\Delta S°$ for reaction (II) with various substituents X are listed in Table II. It will be noted that $\Delta S°$ is large (an increase in $\Delta S°$ of 4.6 cal./deg. corresponds to a tenfold increase in K) and that ΔH is several times larger than $\Delta G°$ as well as opposite in sign in most cases.

The frequently made assumption that the effect of a change in structure upon free energy and upon heat of reaction must necessarily be identical is therefore contrary to the experimental evidence as well as unfounded in theory. The assumption that either experimental quantity may always be taken as a measure of the potential energy change ΔE_p is equally unjustified. It would consequently be entirely incorrect to argue from the free-

energy data of Table II that the substitution of a carboxyl or halogen group makes the binding of bromine to carbon weaker or increases the resonance energy of the central ring in phenanthrene. It would be quite as incorrect to argue from the heats of reaction that these substituents have an opposite effect.

The Ionization of Acids.—Strictly speaking, any consideration of equilibrium in a reaction in solution must include the molecules of the solvent, at least in so far as their potential energy or the kinetic energy of their motions is affected by the presence of the solute molecules. This effect is especially important in reactions involving ions because the very existence of ions in solution is intimately connected with powerful interactions between ions and solvent molecules (page 39). A possible and, in the case of the Debye-Hückel theory of electrolytes, satisfactory approximation to this difficult problem is to treat the interaction between ion and solvent in terms of the energy of a charged body in a dielectric medium. A spherical body of radius r which carries a charge e evenly distributed over its surface and which is immersed in a medium of dielectric constant ϵ possesses an electrostatic energy E_{el} given by

$$E_{el} = \frac{e^2}{2\epsilon r} \tag{38}$$

If it were possible to treat the ions A_1 and A_2 in the reaction

$$HA_1 + A_2^- \rightleftharpoons A_1^- + HA_2 \tag{IV}$$
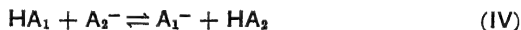
as spheres of this sort, the free-energy change of the reaction would be the sum of an energy change independent of the medium ΔE_n and the electrostatic energy change; hence,

$$\Delta G^\circ = -RT \ln K = \Delta E_n + \frac{Ne^2}{2\epsilon}\left(\frac{1}{r_1} - \frac{1}{r_2}\right) \tag{39}$$

Real ions like acetate or benzoate are not, however, spherical, nor is their distribution of charge symmetrical. In acetate ion the charge is largely concentrated on the carboxylate group, in benzoate ion it is partly distributed over the benzene ring (page 56). An exact analysis of so complicated a situation must be very difficult, but certain features of the result are easily determined. The electrostatic energy is greater, the more

highly concentrated the charge; acetate ion must therefore have a larger value than benzoate ion. To a first approximation it varies inversely as the dielectric constant, and to this approximation equation (39) may be replaced by

$$-RT \ln K = E_n + \frac{A}{\epsilon} \qquad (40)$$

in which A is a function of the size, shape, and charge distribution of the ions A_1 and A_2. The approximation is inexact because the distribution of charge on the ion must be affected by the dielectric constant of the medium in which it is immersed.

Another approach to the same problem is by way of the dipole field of the substituent. If the ions A_1 and A_2 are p-chlorbenzoate and benzoate, respectively, the C—Cl group possesses a dipole moment by virtue of which the work required to transfer a proton from chlorbenzoic acid to benzoate ion includes an electrostatic energy which is given to a first approximation by

$$E_{el} = \frac{e\mu \cos \theta}{\epsilon r^2} \qquad (41)$$

in which $\mu \cos \theta$ is determined by the magnitudes and directions in space of the dipole moments of the C—Cl and the C—H groups and r is the distance from the substituent to the ionizable proton.

To a much better approximation the dielectric constant of the solvent may be replaced by an effective dielectric constant which takes account of the fact that the lines of force from substituent to proton proceed partly through the ion itself, which has a low dielectric constant, and partly through the solvent medium, which has a high one.[7] The magnitude of the effective dielectric constant depends upon the shape and size of the ion and has been calculated for certain favorable cases.

Either approximation, that represented by equation (39) or that of equation (41), predicts that the free energy of a reaction of the type of (IV) should be a linear function of $1/\epsilon$, a prediction

[7] KIRKWOOD and WESTHEIMER, *J. Chem. Phys.*, **6**, 506 (1938). WESTHEIMER and KIRKWOOD, *ibid.*, **6**, 513 (1938). WESTHEIMER and SHOOKHOFF, *J. Am. Chem. Soc.*, **61**, 555 (1939).

that is approximately satisfied by the experimental data.[8] Figure 2, based on recent data,[9] plots the values of

$$\log K = -\frac{\Delta G°}{(2.303RT)}$$

against $1/\epsilon$ for a series of reactions of the type

$$HA + C_6H_5COO^- \rightleftharpoons A^- + C_6H_5COOH \tag{V}$$

K is, therefore, equal to the ionization constant of the acid HA divided by that of benzoic acid, and the problem is that of the
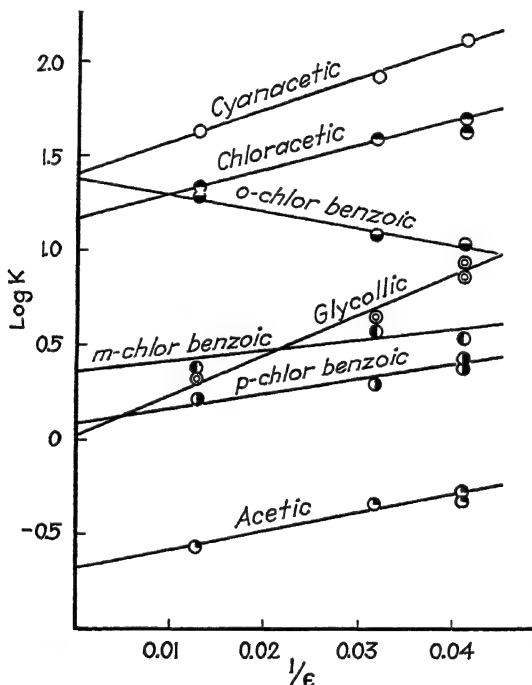
FIG. III-2.—Variation of relative strengths of acids with dielectric constant.[9]

effect of structure on the equilibrium of the ionization of an acid, not that of the absolute properties of the equilibrium itself. The points at an abscissa of 0.0128 were obtained from measurements in water, those at 0.0317 from methanol, and those at 0.041 from

[8] Wynne-Jones, *Proc. Roy. Soc.* (London), **A140**, 440 (1933).

[9] Minnick and Kilpatrick, *J. Phys. Chem.*, **43**, 259 (1939).

measurements in ethanol, in a dioxane-water mixture of the same dielectric constant, or from both sources. Points for salicylic acid, almost coincident with those for chloracetic acid, are omitted as are also points for two phenols, the 2,4- and 2,6-dinitro derivatives. For the carboxylic acids the linearity predicted is approximately satisfied, and the points for the two quite different media of the same dielectric constant do not differ widely. The data for the phenols, on the other hand, show wide disagreement. When the HA in equation (V) is 2,4-dinitrophenol, log K has the value 0.191 in water, 1.559 in methanol, 1.921 in ethanol, and 1.451 in the dioxane-water mixture. Apparently the approximations involved in equation (40) or (41) are valid only when the structure of the ionizing group is the same in the two acids concerned.

Because the dielectric constant is a function of temperature, the introduction of an energy dependent upon the dielectric constant into the Boltzmann expression leads to new complications in the treatment of heats and entropies of reaction. In the favorable case where the partition functions involving the internal kinetic energies cancel between reactants and products, so that the Boltzmann expression takes the form

$$K = e^{-(E_n + A/\epsilon)/RT} \tag{42}$$

the free energy is given by

$$\Delta G^\circ = E_n + \frac{A}{\epsilon} \tag{43}$$

The heat of reaction, obtained by differentiation of ln K [equation (25)], is given by

$$\Delta H = \Delta E_n + \frac{A}{\epsilon} + T\frac{A}{\epsilon^2}\frac{d\epsilon}{dT} \tag{44}$$

and differs from the free energy by virtue of the last term. The entropy is therefore not zero but[10]

$$\Delta S^\circ = \frac{A}{\epsilon}\frac{d\ln\epsilon}{dT} \tag{45}$$

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[10] (a) HAMMETT, *J. Chem. Phys.*, **4**, 613 (1936). (b) GURNEY, *ibid.*, **6**, 499 (1938).

An especially simple case arises when the nonelectrostatic energy E_n is negligible compared with the electrostatic energy A/ϵ, for then

$$\Delta G^\circ = \frac{A}{\epsilon} \tag{46}$$

and

$$\Delta S^\circ = \Delta G^\circ \frac{d \ln \epsilon}{dT} \tag{47}$$

The factor $(d \ln \epsilon)/dT$ has the value of -0.005 in water.

Table III shows that ΔS° is in fact close to $-0.005\Delta G^\circ$ for reactions of the type

$$XC_6H_4COOH + C_6H_5COO^- \rightleftharpoons XC_6H_4COO^- + C_6H_5COOH \tag{VI}$$

provided that X is a meta or a para substituent (first five items of the table). On the other hand, the relation most certainly fails for ortho substituents. Table IV shows that it is likewise invalid for reactions of the type

$$RCOOH + HCOO^- \rightleftharpoons RCOO^- + HCOOH \tag{VII}$$

The data used in Table IV[11a] represent the only precise information available on heats and entropies of ionization. However

TABLE III.—EFFECT OF SUBSTITUENTS ON THE IONIZATION OF BENZOIC ACID[10a] DATA FOR 25°C.

Acid XC_6H_4COOH	K	ΔG°	ΔH	ΔS°	$-0.005\Delta G^\circ$	$\Delta \log K$
m-NO$_2$ benzoic	5.24	$-$ 980	$+$ 350	$+4.5$	$+$ 4.9	-0.35
m-I benzoic	2.00	$-$ 410	$+$ 90	$+1.7$	$+$ 2.1	-0.22*
m-CH$_3$ benzoic	0.85	$+$ 100	$+$ 120	0.0	$-$ 0.5	$+0.04$
p-OCH$_3$ benzoic	0.50	$+$ 410	$+$ 110	-1.0	$-$ 2.1	$+0.12$
p-CH$_3$ benzoic	0.68	$+$ 230	$+$ 210	0.0	$-$ 1.2	$+0.04$
o-NO$_2$ benzoic	96.4	-2690	-2960	-0.9	$+13.5$	$+0.27$
o-OH benzoic	15.6	-1630	$+$ 670	$+7.7$	$+$ 8.2	-0.27
o-I benzoic	19.8	-1770	-2310	-1.8	$+$ 8.9	
o-Cl benzoic	19.3	-1750	-2290	-1.8	$+$ 8.8	$+0.28$
o-CH$_3$ benzoic	1.93	$-$ 390	$+1230$	-2.8	$+$ 2.0	$+0.28$

* This is the value for m-Cl benzoic. The value for m-I benzoic should be nearly identical.

[11] (a) HARNED and EMBREE, *J. Am. Chem. Soc.*, **56**, 1042 (1934). HARNED and EHLERS, *ibid.*, **54**, 1350 (1932); **55**, 652; 2379 (1933). HARNED and SUTHERLAND, *ibid.*, **56**, 2039 (1934). WRIGHT, *ibid.*, **56**, 314 (1934); NIMS, *ibid.*, **58**, 987 (1936). NIMS and SMITH, *J. Biol. Chem.*, **113**, 145 (1936). (b) SCHALLER, *Z. physik. Chem.*, **25**, 497 (1898).

the data of Table III derive from measurements by a single careful investigator[11b] under constant conditions and in the

TABLE IV.—EFFECT OF STRUCTURE ON THE IONIZATION OF ALIPHATIC ACIDS[10a] DATA FOR 25°C.

Acid RCOOH	K	$\Delta G°$	ΔH	$\Delta S°$	$-0.005\Delta G°$	$\Delta \log K$
Acetic	0.0990	+1372	− 99	−4.94	−6.9	+0.13
Propionic	0.0754	+1533	− 155	−5.67	−7.7	+0.40
Butyric	0.0855	+1460	− 678	−7.17	−7.3	+0.37
Chloracetic	7.78	−1216	−1157	+0.20	+6.1	+0.27
Glycollic	0.833	+ 109	+ 223	+0.38	+0.55	
Lactic	0.775	+ 147	− 14	−0.64	−0.74	

same apparatus. Under these conditions many of the errors vanish that might affect the results as absolute measures of ionization constant or of heat of ionization, for only ratios of ionization constants and differences in heats of ionization are involved.

More generally, equation (42) and its corollaries predict a relation between the effect of a change in the solvent at constant temperature and the effect of a change in temperature in a constant solvent. Differentiation of equation (42) with respect to ϵ leads to

$$\frac{\partial \ln K}{\partial \epsilon} = \frac{A}{RT\epsilon^2} \tag{48}$$

from which together with equation (45)

$$\frac{\Delta S°}{\partial \ln K/\partial \epsilon} = RT \frac{d\epsilon}{dT} \tag{49}$$

In this equation the parameter A, the only quantity that depends upon the nature of the acid, has disappeared. Unfortunately, no exact figures for the quantity $(\partial \ln K)/\partial \epsilon$ are available, but quantities are known that are proportional to these derivatives. These are the differences between the values of $\log K$ in water and in butyl alcohol[12] listed as $\Delta \log K$ in Tables III and IV. Since the measurements in butyl alcohol were made in the presence of much lithium chloride (page 94), a large salt effect is superimposed upon the effect of the change in dielectric con-

[12] WOOTEN and HAMMETT, *J. Am. Chem. Soc.*, **57**, 2289 (1935).

stant. The salt effect arises, according to the theory of Debye and Hückel, from the tendency of an ion to cluster ions of opposite charge around itself and to build up an *ionic atmosphere* of predominantly opposite charge. The electric field due to the atmosphere acts to lower the energy of the ion, which, according to equation (40) or (41), is the same effect that an increase in dielectric constant would have. Consequently, measurements made in the presence of a high concentration of ions in butyl alcohol are equivalent to measurements made at low ionic

Fig. III-3.—Comparison of relative entropies of ionization of benzoic acid derivatives with the effect of changing medium on relative acid strength.

strength in a solvent of appreciably higher dielectric constant. The difference in log K between water and butyl alcohol must therefore be proportional to $(\partial \ln K)/\partial \epsilon$ although the proportionality constant is unknown.

Figure 3 shows that a plot of $\Delta S°$ against $\Delta \log K$ does approximate moderately well to a straight line through the origin for the aromatic acids of Table III, including the ortho substituted ones. As predicted from equation (49) and the fact that $d\epsilon/dT < 0$, the slope is negative. Salicylic acid, which deviates widely, has been omitted from this plot because of the considerable evidence that chelate hydrogen bonding is a complicating factor of importance in its behavior.[13] Figure 4, on the other

[13] BRANCH and YABROFF, *J. Am. Chem. Soc.*, **56**, 2568 (1934).

hand, shows a complete lack of correlation in the case of the aliphatic acids of Table IV. The probable conclusion to be drawn from these results is that the internal kinetic energies are equal for reactants and products in a reaction of the type of equation (VI) when it is a question of a substitution in the benzene ring but that such a compensation does not exist in the aliphatic compounds. It is not, therefore, possible to conclude from the fact that acetic acid is weaker than formic that the sub-
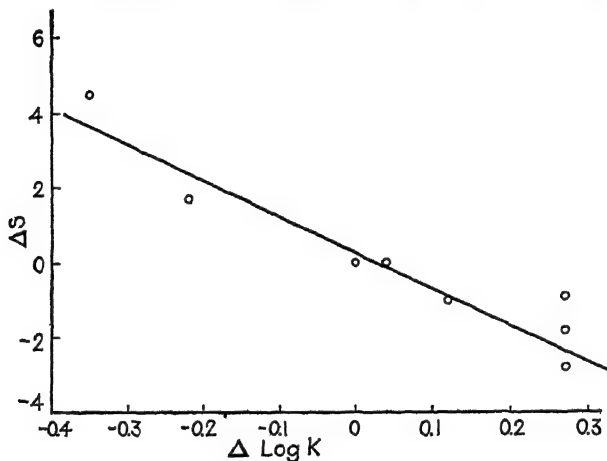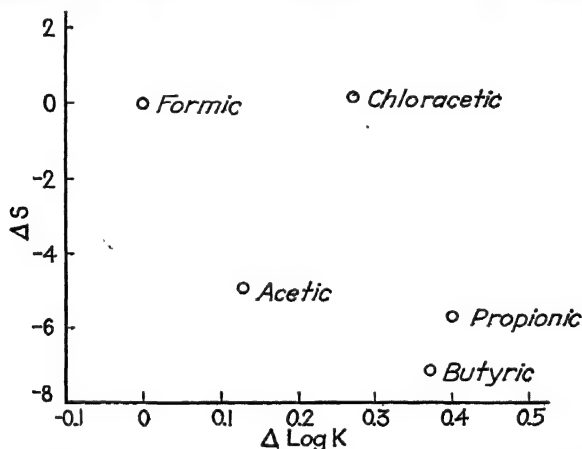

Fɪɢ. III-4.—Comparison of relative entropies of ionization of aliphatic acids with the effect of changing medium on relative acid strength.

stitution of methyl for hydrogen increases the electron density at the O—H linkage and binds the hydrogen ion more firmly: the problem is much too complex to permit so simple an analysis.

With respect to the aromatic acids, it may be concluded that practically the whole effect of a meta or para substituent is exerted by way of the change in electrostatic energy, whereas an ortho substitution involves also a large change in a nonelectrostatic energy. The relative simplicity of the effect observed with the meta and para substituted acid is a phenomenon of very general occurrence in the behavior of benzene derivatives (pages 121, 184).

Activities and Activity Coefficients.—The treatment given thus far has neglected deviations from ideality. The exact thermodynamic expression for the equilibrium in the reaction

$$A + B \rightleftharpoons C + D \tag{VIII}$$

is[3]

$$\frac{a_C a_D}{a_A a_B} = K \qquad (50)$$

in which the a's are *activities*. The activity of a substance is defined fundamentally in terms of the statement that the quantity $RT \ln a$ represents the work that can be gained by the reversible transfer of one mole of the substance from the state in which it exists to some standard or reference state at the same temperature. Any force of interaction that tends to bind the substance to other components of the solution must therefore decrease its activity, for the work that must be done against these forces decreases the amount that becomes available when the substance is transferred to the reference state.

The activity of a substance may be determined in a variety of ways of which the simplest depends upon the principle that the ratio of the activities of a substance in two different solutions at a given temperature is equal to the ratio of its partial vapor pressures from the two solutions, provided that the pressures are so low that the perfect gas laws apply to the vapors. In a very dilute solution the activity of a solute has been found to be very nearly proportional to its concentration except in the case of electrolytes and of partly associated substances.

The ratio of activity to concentration is a very useful quantity, the *activity coefficient*. It is usually represented by the symbol f (which must not be confused with the use of the same symbol for the partition function). Its definition is

$$f = \frac{a}{c} \qquad (51)$$

In ideal solutions, those in which activity is proportional to concentration, f is constant; in others, its variation measures the extent of the deviation from ideality. Substitution of the definition (51) and obvious rearrangement converts equation (50) to

$$\frac{[C][D]}{[A][B]} = K \frac{f_A f_B}{f_C f_D} \qquad (52)$$

It follows that the equilibrium equation in terms of concentrations instead of activities is valid only within a range of systems

for which the activity coefficients of the reactants remain constant. This is true if the solution in which the reaction occurs is very dilute and the solvent is constant. It is not, in general, true when any significant change occurs in the medium in which the reaction occurs. Table V shows how K_c, the ratio of the concentrations at equilibrium of the enol and keto forms of benzoylcamphor, varies with changing solvent. By equation (52) this quantity is given by

$$K_c = \frac{[\text{E}]}{[\text{K}]} = K\frac{f_{\text{K}}}{f_{\text{E}}} \tag{53}$$

in which f_{E} is the activity coefficient of the enol form, f_{K} that of the keto, and K is constant for all the solutions.

A high value of f indicates a low solubility, for the vapor pressure of solute from any saturated solution is necessarily equal to that of the pure solute. A low solubility implies, therefore,

TABLE V.—KETO-ENOL EQUILIBRIUM AND SOLUBILITY OF BENZOYLCAMPHOR[14]

Solvent	K_c	R	K_c/R
Ether	6.81	6.39	1.06
Ethyl acetate	1.98	1.81	1.09
Ethanol	1.67	1.57	1.06
Methanol	0.869	0.748	1.15
Acetone	0.852	0.80	1.06

a large ratio of vapor pressure or activity to concentration, *i.e.*, a large activity coefficient. Consequently, a solvent in which the enol is relatively soluble tends to have a large value of K_c, one in which the keto form is relatively soluble to have a small value. In favorable cases this parallelism may become a fairly exact proportionality between K_c and the ratio of the solubilities. This is shown in Table V in which the quantity R is the solubility of enol divided by that of keto, and the ratio in the last column is satisfactorily constant.

Medium and Salt Effects in Ionic Reactions.—When the reacting substances or some of them are ions, the value of K_c becomes especially sensitive to changes in the medium in which

[14] DIMROTH, *Ann.*, **399**, 91 (1913). Values of K_c for other diketones and keto acids in a variety of solvents are given by Meyer, *Ber.*, **45**, 2846 (1912).

the reaction occurs, for such changes have large effects upon the activity coefficients of ionic substances.   The activity coefficient of an ion decreases rapidly with increasing ion concentration or, more exactly, with increasing ionic strength.   The *ionic strength* μ is one-half the sum of the concentrations of the various ions present, the concentration of each ion being multiplied by the square of its charge z

$$\mu = \frac{1}{2}\sum^{i} c_i z_i^2 \tag{54}$$

The dependence of μ on z^2 indicates the large effect produced by doubly and triply charged ions.

In very dilute solutions in a solvent of high dielectric constant like water, the variation of activity coefficient with ionic strength is the same for all ions of a given charge and is given, according to the theory of Debye and Hückel, by

$$\log f = -az^2\sqrt{\mu} \tag{55}$$

in which a is a known function of temperature, dielectric constant, and universal constants.   At higher ionic strengths the rate of decrease becomes smaller than that given by this equation, and the activity coefficient may even go through a minimum and begin to increase; the value is now different for different ions. A satisfactory empirical equation is

$$\log f = -az^2\sqrt{\mu} + b\mu \tag{56}$$

with b an empirical constant with a characteristic value for each ion.   The minimum value of f for univalent ions is 0.6 to 0.8, and the ionic strength at which the minimum appears, 0.7 to 2.

The deviation from ideality that this variation of f implies is attributed to forces of attraction between the oppositely charged ions, which are more important than the repulsions between the like charged ions and which increase in magnitude as the concentration increases and the average distance between the ions decreases.   By similar reasoning a decrease in the dielectric constant of the medium, such as is produced by the substitution of alcohol for water, leads to an increase in the activity coefficient, for it increases the electrostatic energy of the ion (page 80).

The latter effect is to a large extent responsible for the low solubility of salts in nonaqueous solvents.

If therefore the substances C and D in reaction (VIII) are ions and A and B are uncharged, the composition of the system at equilibrium tends to shift in the direction of increased proportions of C and D when the ionic strength of the solution is increased by the addition of electrolyte. It will tend to shift in the other direction when the ·dielectric constant is decreased by a change in the composition of the solvent. Both these effects follow from equation (52) and the nature of the changes in f that have just been discussed. More generally, the same effects must appear whenever C and D carry a greater density of charge than A and B, specifically when

$$z_C^2 + z_D^2 > z_A^2 + z_B^2 \qquad (57)$$

where the z's are the charges.

Salt Effects on Indicators.—The most easily appreciated case of this sort is that of a reaction involving an indicator. In spite of the pages of discussion to which misapprehensions and misunderstandings have given rise, an indicator remains in principle what Ostwald pointed out many years ago, *viz.*, an acid or a base the ionization of which is accompanied by a change in light absorption in the visible region of the spectrum.[15] The Brønsted nomenclature perhaps specifies it more elegantly in defining an indicator as a conjugate acid-base system in which the colors of the acid and base are different. Thus the acid p-nitrophenol (A) is colorless, and its conjugate base (B) is

$$\underset{(A)}{O_2NC_6H_4OH} \qquad \underset{(B)}{[O_2NC_6H_4O]^-}$$

intensely yellow. The question as to why these substances differ in color is part of the more general problem of the usual difference in light absorption between acid and conjugate base (page 51); it has nothing whatsoever to do with the application as an indicator. For this, the sufficient fact is that the equilibrium constant of the reaction

$$A + H_2O \rightleftharpoons B + OH_3^+ \qquad (IX)$$
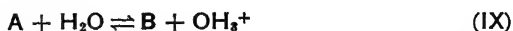
[15] The indicator problem is excellently discussed by Kolthoff, "Acid-base Indicators," New York, 1937.

is given by

$$\frac{[B][OH_3^+]}{[A]} = K_c \tag{58}$$

or

$$\frac{[A]}{[B]} = \frac{1}{K_c}[OH_3^+] \tag{59}$$

and that the ratio [A]/[B] can be determined by colorimetric methods. If K_c is known, the colorimetric measurement leads, therefore, directly to a value of the concentration of oxonium ion, *i.e.*, of the acidity of the solution. All applications of indicators depend upon equation (59) or upon similar and easily derived ones.

Dimethylaminoazobenzene has a yellow uncharged base (C),

$$(CH_3)_2\bar{N} - C_6H_4 - \bar{N} = \bar{N} - C_6H_5 \qquad [(CH_3)_2N = C_6H_4 = \bar{N} - \bar{N}H - C_6H_5]^+$$
$$(C) \qquad\qquad\qquad (D)$$
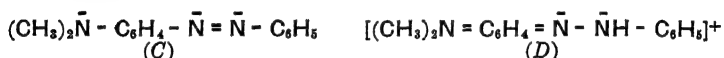
the positively charged conjugate acid is red and has a probable structure[16] which may be approximately represented by (D). Its sulfonic acid derivative methyl orange possesses the structures (E) and (F) as base and acid

$$[(CH_3)_2\bar{N} - C_6H_4 - \bar{N} = \bar{N} - C_6H_4SO_3]^- \quad (CH_3)_2N = C_6H_4 = \bar{N} - \bar{N}H - C_6H_4SO_3$$
$$(E) \qquad\qquad\qquad\qquad (F)$$
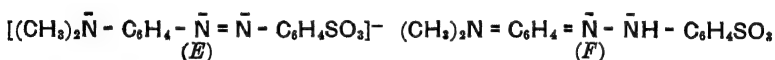
Both the quality of the color change and the value of the constant K_c are nearly identical with those of the unsulfonated substance. The electrically neutral acid is a dipolar ion with a positive charge on the $(CH_3)_2N$ and a negative one on the SO_3 group.

In phenolphthalein and the sulfonphthaleins the color change accompanies the conversion of the colorless singly negative ion

$$(G) \qquad\qquad\qquad\qquad (H)$$
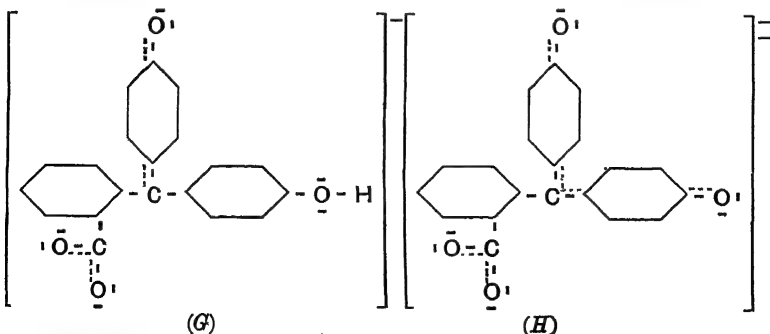
[16] HANTZSCH and VOGT, *Ber.*, **62B**, 968 (1929).

(G) to the doubly negative ion (H). The symmetrical resonance in (H) is responsible for the relatively high acidity of the phenolic proton in (G) and for the intensity of the color.[17]

For an indicator I of the electrical type of aminoazobenzene in equilibrium with a weak acid HA of the acetic acid type

$$I + HA \rightleftharpoons IH^+ + A^- \tag{X}$$

the law of equilibrium takes the form[18]

$$\frac{[IH^+][A^-]}{[I][HA]} = K \frac{f_I f_{HA}}{f_{IH^+} f_{A^-}} \tag{60}$$

The addition of sodium chloride or other inert electrolyte decreases the values of f_{IH^+} and f_A. Since these are in the denominator, the fraction involving the f's increases, and to maintain equality the fraction involving the concentrations must also increase. Thus the effect of the addition of salt is to shift the color of the solution toward that of the acid form of the indicator. The solution appears to be more acid, and in a sense it is because the equilibrium

$$HA + H_2O \rightleftharpoons OH_3^+ + A^- \tag{XI}$$
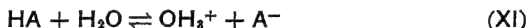
must likewise be shifted in the direction of a higher concentration of OH_3^+. The substitution of alcohol for part of the solvent must, on the other hand, decrease the apparent acidity because it increases the ionic activity coefficients.

In a solution containing acetic acid HA and p-nitrophenol HI on the other hand, the equilibrium follows the law

$$\frac{[HI][A^-]}{[I^-][HA]} = K \frac{f_I \cdot f_{HA}}{f_{HI} f_{A^-}} \tag{61}$$

Since the effect of changing medium is nearly the same for all ions of a given charge type, the effect upon the two ionic activity coefficients in equation (61) will nearly cancel, whereas the effect upon the coefficients of the uncharged molecules is relatively small. Consequently, there is little change in color upon the addition of sodium chloride or alcohol to such a system, although the change in the oxonium-ion concentration is the same as when aminoazobenzene is used as the indicator. All these effects are easily observable and have been subjected to quantitative measurement.[18]

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[17] Ref. 42, Chap. II.

[18] BRØNSTED, *J. Chem. Soc.*, **119**, 574 (1921). See also Ref. 15.

Unfortunately for theoretical treatment, many of the commonest indicators contain sulfonate or other solubilizing groups, as is the case with methyl orange. The reacting substances contain, therefore, two or more charged groups, distributed at greater or less distances over a large molecule. The problem of predicting salt or medium effects in such cases is a difficult one in which, however, some progress has been made.[19]

The Suppression of Salt Effects.—If one wishes to isolate a particular equilibrium or a series of equilibria for study, *e.g.*, to compare the strengths of a series of acids, the salt effect may be a great nuisance. One way to eliminate it is to measure the ionization constant K_c at various ionic strengths and, by extrapolation, to estimate the limit approached as the ionic strength approaches zero. This is the *method of dilute solutions*, which has always been widely used in the theoretical treatment of electrolytes. Another and frequently more useful procedure[20] is to *suppress* the salt effect by introducing into all the solutions under investigation a large concentration of an electrolyte that is not involved in the equilibrium and does not react with any of the substances that are involved. Sodium chloride may, for instance, be used with aqueous acetic acid, for neither sodium nor chloride ions react appreciably with acetic acid, acetate ion, or oxonium ion. The slope $df/d\mu$, which determines the magnitude of the change in activity coefficient produced by a given change in ionic strength, has its greatest magnitude in dilute solution and is zero in the region ($\mu = ca$ 0.75) where f is at a minimum (page 90). Consequently, the salt effect is smallest in this region of ionic strength and may be said to be suppressed by the large concentration of inert electrolyte. As a further refinement, one may vary the concentration of inert electrolyte to balance the differences in concentration of reacting electrolyte in the solutions under investigation so that all of them have the same ionic strength (page 216).

On Reaction Mechanisms.—If one assumes that the neutralization of ammonia by an acid in aqueous solution consists in the

[19] GÜNTELBERG and SCHIÖDT, *Z. physik. Chem.*, **135**, 393 (1928). KOLTHOFF and GUSS, *J. Am. Chem. Soc.*, **60**, 2516 (1938).

[20] BRØNSTED, *Medd. K. Vetenskapsakad. Nobelinst.* **5,** 1 (1919). BRØNSTED and PEDERSEN, *Z. physik. Chem.*, **103,** 307 (1922).

direct transfer of a proton

$$NH_3 + OH_3{}^+ \rightleftharpoons NH_4{}^+ + H_2O \qquad (XII)$$
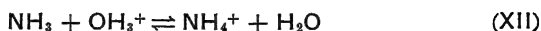
then the law of equilibrium gives

$$\frac{a_{NH_4{}^+}a_{H_2O}}{a_{NH_3}a_{OH_3{}^+}} = K \qquad (62)$$

If, however, one assumes that the process involves the hydration and ionization of the ammonia followed by the reaction of the hydroxyl ion with oxonium ion

$$NH_3 + H_2O \rightleftharpoons NH_4OH \qquad (XIII)$$
$$NH_4OH \rightleftharpoons NH_4{}^+ + OH^- \qquad (XIV)$$
$$OH^- + OH_3{}^+ \rightleftharpoons 2H_2O \qquad (XV)$$
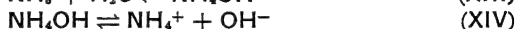
the application of the law of equilibrium leads to the equations

$$\frac{a_{NH_4OH}}{a_{NH_3}a_{H_2O}} = K_1 \qquad (63)$$

$$\frac{a_{NH_4{}^+}a_{OH^-}}{a_{NH_4OH}} = K_2 \qquad (64)$$

$$\frac{a^2{}_{H_2O}}{a_{OH^-}a_{OH_3{}^+}} = K_3 \qquad (65)$$

Since these all refer to a single solution, the symbol a_{NH_4OH}, which appears in the first two equations, represents the same quantity in both and will cancel if the equations are multiplied together. Consequently, multiplication of the three equations leads to the relation

$$\frac{a_{NH_4{}^+}a_{H_2O}}{a_{NH_3}a_{OH_3{}^+}} = K_1 K_2 K_3 \qquad (66)$$

The fact that the quantity that appears on the left side of equations (62) and (66) is experimentally a constant is therefore just as consistent with the reaction mechanism represented by equations (XIII), (XIV), and (XV) as it is with the direct proton transfer of equation (XII) and offers no criterion of distinction between them.

This conclusion is indeed a necessary consequence of fundamental thermodynamic principles and is perfectly general. *A study of the equilibrium state of a system can offer no pertinent information whatsoever with respect to the mechanism by which that equilibrium is attained*; this problem can be attacked only by investigation of the kinetics of the reaction.

CHAPTER IV

REACTION RATES AND MECHANISMS: ENERGIES, FREE ENERGIES, AND ENTROPIES OF ACTIVATION

The Fundamental Principle of Reaction-rate Theory.—There is no branch of physical chemistry of greater importance and interest to the organic chemist than that of reaction rates. The selection of the proper conditions for a synthetic operation is usually a problem in reaction rates, and the study of the rates of reaction is the most useful tool available for the investigation of reaction mechanisms, the problem which more than any other theoretical one has excited the imagination of organic chemists.

The basic assumption of all reaction-rate investigations is the principle that the rate of a reaction, *i.e.*, the number of moles reacting in unit time, is proportional to the product of the concentrations of the reacting substances and independent of the concentrations of substances that do not take part in the reaction, provided that the medium in which the reaction occurs is reasonably constant. This principle is a most reasonable one in terms of the extremely probable hypothesis that the rate of a reaction is proportional to the frequency of the collisions between the reacting molecules, which is itself proportional to the product of the concentrations. It is an experimentally verifiable fact in many reactions; the assumption that it also applies in the apparent exceptions has proven a most fruitful one. A classical example of this sort, the investigation of which by Lapworth[1] initiated a new kinetic era in theoretical organic chemistry, is the halogenation of acetone and other ketones. The actual process that occurs, the stoichiometric reaction, is

$$CH_3 \cdot CO \cdot CH_3 + Br_2 \rightarrow CH_3 \cdot CO \cdot CH_2Br + Br^- + H^+ \qquad (I)$$

The rate is proportional to the concentration of acetone, as expected, but it is independent of the concentration of bromine; *i.e.*, an increase in the concentration of the bromine leads to no

[1] LAPWORTH, *J. Chem. Soc.*, **85**, 30 (1904).

increase in rate of reaction. Furthermore, the rate is increased by the addition of either acids or bases, and the increase in rate is proportional to the concentration of acid or base, in spite of the fact that these substances do not appear in the stoichiometric equation. The general principle can, however, be reconciled with the specific problem by the assumption that the reaction of equation (I) is composed of a series of steps of the following sort:

$$CH_3 - \overset{\overset{\bar{O}}{|}}{\underset{\underset{CH_3}{|}}{C}} + B \rightleftharpoons \left[CH_3 - \overset{\overset{O}{||}}{C} {\cdots} CH_2 \right]^- + BH^+ \qquad (II)$$

$$\left[CH_3 - \overset{\overset{O}{||}}{C} {\cdots} CH_2 \right]^- + \cdot \bar{Br} - \bar{Br} \cdot \rightarrow CH_3 - \overset{\overset{\bar{O}}{|}}{\underset{\underset{CH_2 - \bar{Br} \cdot}{|}}{C}} + [\cdot \bar{Br} \cdot]^- \quad (III)$$
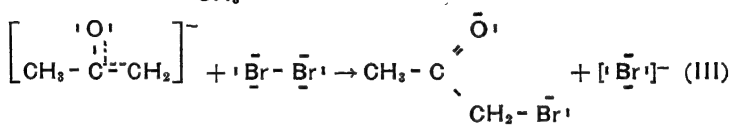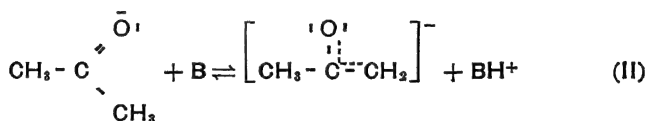
in which B is a base, which might be hydroxyl or acetate ion, pyridine, water, or the like. If the tendency of bromine to react with the ion is so great that every ion formed reacts practically instantaneously, the rate of the system of successive reactions, reactions (II) and (III), becomes that of the first step reaction (II). But reaction (II) does not involve bromine, therefore its rate must be independent of the concentration of bromine; it does involve the base B, therefore its rate must be proportional to the concentration of the base. Reaction (II) is said, consequently, to be the *rate-determining step* of the bromination, and the system of reactions is said to constitute a possible *mechanism* for process (I).

This mechanism has been verified in a variety of ways. The rate of reaction of acetone with iodine is identical with its rate of reaction with bromine under similar conditions.[1,2] This is

$$C_6H_5 - CO - CHR'R''$$

$$(A) \qquad\qquad (B)$$
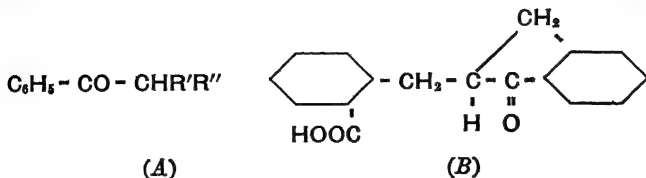
[2] BARTLETT, *J. Am. Chem. Soc.*, **56**, 967 (1934).

consistent with the mechanism, in which neither halogen enters into the rate-determining step. Further support has been obtained from the racemization and the deuterium uptake of ketones. If an optically active ketone of the structure (A) reacts with a base according to equation (II), the carbanion formed has only three groups attached to carbon, and these tend strongly to take up a planar and symmetrical configuration (page 66). Since the proportion of ion is at all times small, reaction (II) must be reversible; but the reversal must produce as much dextro- as levo-rotatory ketone if the ion is symmetrical. The detailed analysis (page 109) shows that the rate of the resulting base-catalyzed racemization must be equal to the rate of reaction (II) and, hence, to that of the halogenation. The experimental test[3] on the ketone B gave for the specific rate of the acetate ion catalyzed bromination in an acetic acid-water solvent the value 0.0471. Under the same conditions the specific rate of the racemization is 0.0438. The result not merely confirms the mechanism of the halogenation, it demonstrates that the carbanion does not retain its configuration.

Finally, the rate at which phenyl-s-butyl ketone exchanges its α-hydrogen for deuterium is very nearly the same as, and is probably identical (if properly corrected for minor complications) with, the rate of racemization under the same conditions.[4] The rate of the exchange is again that of reaction (II), but a deuteron rather than a proton is added when the ion reverts to ketone.

The apparent exception to the general principle that rate of reaction is proportional to the product of the concentrations of the actual reactants has, therefore, been completely and satisfactorily accounted for in terms of a *mechanism* involving more than one step, to each of which the principle applies. If the principle is accepted as demonstrated on the basis of this kind of evidence, it becomes a most powerful implement for the investigation of the mechanism of reaction. A mechanism thus derived is a scientific tool by which to obtain verifiable relationships between measurable quantities; it is to be judged by its utility in correlating known facts and predicting new ones, not by its agreement with some unknowable absolute truth. By this

[3] Hsü and Wilson, *J. Chem. Soc.*, 623 (1936).

[4] Hsü, Ingold, and Wilson, *J. Chem. Soc.*, 78 (1938).

criterion the mechanism of these ketone reactions must be recognized as known with a truly remarkable degree of certainty.

Reaction Orders and Their Determination.—In order to investigate the mechanism of a reaction it is necessary to determine the order of the reaction, which means the number of concentration factors appearing in the equation for the rate. The obvious method of accomplishing this is to vary the concentrations of the possible reactants and to determine the effect of these changes. The actual rate is, however, not directly measurable; and, since it changes as a result of the changing concentrations of the reactants during the course of the reaction, it is not sufficient to divide the decrease in concentration in a given time interval by that interval, the limiting value of this ratio, $-dc/dt$ must be used. To obtain this derivative, one can of course plot concentration against time and estimate the slope graphically, but the procedure is so inaccurate that it is applied only as a last resort. Preferably, integrated equations based upon various orders are applied to the data until one is found that fits. If a reaction is of the first order, the rate is given by

$$-\frac{dc}{dt} = kc \qquad (1)$$

The proportionality constant k is called the *rate constant* or the *specific rate*. The latter term derives from the fact that k is equal to the actual rate divided by the concentration of the reactant (by the product of the concentrations of the reactants for higher orders than the first). It is the value that the rate takes when all the reactant concentrations are unity. Equation (1) is easily integrated yielding

or
$$\left.\begin{array}{l} \ln c_0 - \ln c = kt \\[2mm] \log c_0 - \log c = 0.4343kt \end{array}\right\} \qquad (2)$$

in which c_0 is the concentration when $t = 0$. From this it follows that a plot of the logarithm of concentration against time is a straight line if the reaction is of the first order. The slope of the line, which may be determined either by graphical or by analytical methods, is equal to $-0.4343k$. Consequently, such a linear plot not only distinguishes a first-order reaction but makes it easy to determine the rate constant.

It is not necessary to plot the actual concentration, any quantity proportional to the concentration may be used even when the proportionality constant is unknown. Such quantities as optical rotation α, pressure in a gas reaction, change in volume in a dilatometer, and shift in the bands in an interferometer are frequently used. If $\alpha = mc$, then $\log \alpha = \log m + \log c$, $\log \alpha_0 = \log m + \log c_0$, equation (2) reduces to

$$\log \alpha_0 - \log \alpha = 0.4343kt \tag{3}$$

and the slope of a plot of $\log \alpha$ against t is again $-0.4343k$.

In the second-order reaction of the two substances A and B the rate of change of one concentration is necessarily equal to that of the other, since one mole of the one substance must react for each mole of the other. By the fundamental principle it is proportional to the product of the concentrations

$$-\frac{d[A]}{dt} = -\frac{d[B]}{dt} = k[A][B] \tag{4}$$

The equation may be simplified before integrating by introducing the symbols a and b for the initial (at time $t = 0$) concentrations of A and B, respectively, and x for the change in concentration at time t. Then

$$\frac{dx}{dt} = k(a - x)(b - x) \tag{5}$$

which integrates to

$$\frac{1}{(b - a)} \ln \frac{a(b - x)}{b(a - x)} = kt \tag{6}$$

The applicability of this equation may be tested and the value of k determined most simply by a plot of $\log \dfrac{(b - x)}{(a - x)}$ against t.

If the initial concentration of one substance in a second-order reaction is much greater than that of the other, e.g., if $b \gg a$, then necessarily $b \gg x$ because x cannot be greater than a. In this case both $b - x$ and $b - a$ become practically equal to b, and equation (6) reduces to

$$\left. \begin{array}{c} \dfrac{1}{b} \ln \dfrac{a}{a - x} = kt \\[2mm] \ln a - \ln (a - x) = bkt \end{array} \right\} \tag{7}$$

or

In view of the meaning of the various symbols this is identical with the equation for a first-order reaction (2) except that the first-order constant of equation (2) is replaced by the product bk of a second-order constant by the concentration b. The reaction may be said to "follow a first-order course" or to be "pseudo first order," but the apparent first-order constant has a value proportional to the concentration of the substance B.

Clearly, one cannot determine the order of a reaction merely by following its course from a given initial concentration. It is necessary to run the reaction with different initial concentrations of all conceivable reactants and to determine whether the apparent constants are really invariable.

When a second-order reaction consists in the reaction of two identical molecules, the rate is proportional to the square of the concentration

$$-\frac{dc}{dt} = kc^2 \tag{8}$$

$$\frac{1}{c} - \frac{1}{c_0} = kt \tag{9}$$

in this case a plot of the reciprocal of the concentration is linear in the time. The same equations apply when the reaction involves two different substances, present at the same concentration.

A test of reaction order with respect to the solvent is impossible because the concentration of the solvent molecules cannot be changed without also changing the nature of the medium in which the reaction occurs. But it is only if the medium is maintained constant that the fundamental assumption of proportionality between concentration and rate is applicable. Consequently, it is impossible to determine by kinetic methods if the solvent takes part in the rate-determining step of a reaction..

On the Units of Time.—There is an unfortunate lack of agreement on the unit of time to be used in presenting kinetic data and even a certain carelessness in making plain what unit is used in a particular investigation. Furthermore, the quantity $0.4343k$ is frequently tabulated instead of k itself, sometimes with, sometimes without adequate warning. All kinetic data in this book are in terms of the second as the unit of time and are values of k, unless accompanied by a specific statement to the contrary.

Reversible Reactions.—The differential equations for a reversible reaction can always be integrated if the order is not greater than two in either the forward or the reverse direction. The resulting equations are considerably simplified by introducing as one of the parameters a quantity determined by the equilibrium state of the system. For the reaction

$$A \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} B \tag{IV}$$

which may be either true or pseudo first order, with the rate constants indicated, the rate of concentration change is given by the difference in the rates in the two directions, each proportional to the concentration of the reacting substance

$$-\frac{d[A]}{dt} = \frac{d[B]}{dt} = k_1[A] - k_{-1}[B] \tag{10}$$

By using the symbols a and b for the initial concentrations of A and B and x for the moles per liter of A converted to B at time t, this becomes

$$\frac{dx}{dt} = k_1(a - x) - k_{-1}(b + x) = (k_1 a - k_{-1} b) - (k_1 + k_{-1})x \tag{11}$$

the integral of which, after substituting the limit $x = 0$ when $t = 0$, is

$$\ln \frac{k_1 a - k_{-1} b}{(k_1 a - k_{-1} b) - (k_1 + k_{-1})x} = (k_1 + k_{-1})t \tag{12}$$

When t increases indefinitely, the reaction comes to a state of equilibrium and x attains a value x_e, which may be expressed in terms of the constants by means of the following considerations. When t becomes infinite, the left side of equation (12) must do so also, and this requires that the denominator approach zero, i.e.,

$$(k_1 a - k_{-1} b) - (k_1 + k_{-1})x_e = 0 \tag{13}$$

Elimination of $k_1 a - k_1 b$ between equations (12) and (13) leads to

$$\ln \frac{x_e}{x_e - x} = (k_1 + k_{-1})t \tag{14}$$

This equation differs from the expression for an irreversible first-

order reaction in two respects. Instead of the initial concentration a of the reactant A in the expression.

$$\ln \frac{a}{a - x} = kt \tag{15}$$

there appears x_e the amount of A that will have reacted when equilibrium is attained; instead of the constant for the forward reaction there appears the sum of the constants for forward and reverse reactions. The procedure for obtaining the sum $k_1 + k_{-1}$ in the reversible case is the same as that for obtaining the constant in the irreversible case: the slope of a plot of log $(x_e - x)$ against time is $-0.4343(k_1 + k_{-1})$.

Here also absolute values of the concentration are unnecessary. If the substances A and B are optically active so that the rotation α is given by

$$\alpha = m[\text{A}] + n[\text{B}] = m(a - x) + n(b + x) = (ma + nb) + (n - m)x \tag{16}$$

the rotation of the equilibrium system α_e is

$$\alpha_e = (ma + nb) + (n - m)x_e \tag{17}$$

and the initial rotation α_0 is

$$\alpha_0 = ma + nb \tag{18}$$

Combination of equations (16) to (18) with equation (14) leads to

$$\ln \frac{\alpha_e - \alpha_0}{\alpha_e - \alpha} = (k_1 + k_{-1})t \tag{19}$$

from which the value of $k_1 + k_{-1}$ may be determined by measurements of rotation as a function of time, without any knowledge of the constants m and n.

If the individual constants k_1 and k_{-1} are to be determined, the equilibrium state must be more completely specified. From equation (13) or more directly from equation (11) by setting $dx/dt = 0$,

$$\frac{b + x_e}{a - x_e} = \frac{k_1}{k_{-1}} \tag{20}$$

A measurement of the value of x_e leads, therefore, to the ratio

k_1/k_{-1}, and, if the sum $k_1 + k_{-1}$ is known, k_1 and k_{-1} are easily calculated.

Equation (20) leads also to an important relation between the rate constants and the thermodynamic equilibrium constant. The latter is given by

$$K = \frac{[\text{B}]}{[\text{A}]} = \frac{b + x_e}{a - x_e} \tag{21}$$

from which with equation (20)

$$K = \frac{k_1}{k_{-1}} \tag{22}$$

Equation (22) is valid regardless of the order of the reactions. This may easily be shown by setting the rate equal to zero in the differential equation for the rate of the reversible reaction and comparing the result with the thermodynamic equation. This very general relation between equilibrium and rate constants is frequently of great utility in kinetic problems.

Mathematics of Consecutive Reactions: The Halogenation of Acetone.—When the order of a reaction is determined, the next step is to consider what mechanisms are consistent with the order. Thus a mechanism involving a direct attack of bromine on acetone is inconsistent with the fact that the rate of the acetone bromination is independent of the bromine concentration. Although one can often make such a short cut in the reasoning as was taken in the discussion of page 97, the safest procedure is to make a complete mathematical analysis of the reaction system involved in each mechanism considered. In the mechanism of equations (II) and (III) for the acetone bromination the first step is a reversible reaction for which the differential equation is

$$\frac{d[\text{K}]}{dt} = -k_1[\text{K}][\text{B}] + k_{-1}[\text{I}][\text{BH}^+] \tag{23}$$

The symbol K is used for acetone, I for the ion $[\text{CH}_3 \cdot \text{CO} \cdot \text{CH}_2]^-$, and Y for bromacetone. The rate of change of the concentration of the ion is the difference between the rates of its formation from acetone and its reaction to form either acetone

or bromacetone

$$\frac{d[I]}{dt} = k_1[K][B] - k_{-1}[I][BH^+] - k_2[I][Br_2] \quad (24)$$

The rate of change of the concentration of bromacetone is simply the rate of formation of the substance from the ion

$$\frac{d[Y]}{dt} = k_2[I][Br_2] \quad (25)$$

because the reaction is practically irreversible. The three differential equations (23), (24), and (25) are not independent since

$$[K] + [I] + [Y] = \text{constant}$$

and

$$\frac{d[K]}{dt} + \frac{d[I]}{dt} + \frac{d[Y]}{dt} = 0 \quad (26)$$

The exact integration of such a system of equations is a difficult problem. It has been solved[5] for the case that all the reactions follow a first-order course, *i.e.*, are first order or pseudo first order. The solution holds not merely for two but for any number of successive steps, but its form is complicated and difficult to apply to experimental data. An approximate solution, which is of high precision in such cases as the one under discussion, may be derived by a method that is usually called the *method of the stationary state*.[6] A better name would be the *method of the unstable intermediate*,[7] since it depends upon all the intermediates being unstable in the sense that their high reactivity makes their concentrations extremely small.

In the acetone bromination the ion I is an intermediate of this sort, since the extent of the acidic ionization of acetone is too small to be detected directly. In order that the concentration of the ion may remain small, the rate of change of its concentration $d[I]/dt$ must be small compared with the rate $k_1[K][B]$ at which it is formed from acetone. This means in view of equation (24) that $d[I]/dt$ is a small difference between relatively large num-

[5] RAKOWSKI, *Z. physik. Chem.*, **57**, 321 (1907).

[6] (a) BODENSTEIN, *Z. Elektrochem.*, **38**, 911 (1932). (b) CHRISTIANSEN, *Z. physik. Chem.*, **28B**, 303 (1935).

[7] SKRABAL, *Monatsh.*, **64**, 289 (1934).

bers and may be neglected in comparison with them. Consequently, equation (24) approximates closely to

$$0 = k_1[K][B] - k_{-1}[I][BH^+] - k_2[I][Br_2] \tag{27}$$

and

$$[I] = \frac{k_1[K][B]}{k_{-1}[BH^+] + k_2[Br_2]} \tag{28}$$

The same considerations applied to equation (26) lead to the approximation

$$\frac{d[K]}{dt} + \frac{d[Y]}{dt} = 0 \tag{29}$$

i.e., the rate of formation of bromacetone is practically identical with the rate of reaction of acetone, the approximation being merely that there is no appreciable storage of reacting material in the form of the intermediates. Introduction of the value of [I] from equation (28) into either equation (23) or (25) leads to

$$-\frac{d[K]}{dt} = \frac{d[Y]}{dt} = \frac{k_1 k_2[K][B][Br_2]}{k_{-1}[BH^+] + k_2[Br_2]} \tag{30}$$

In order that this expression for the rate may be independent of the bromine concentration, it is necessary and sufficient that

$$k_2[Br] \gg k_{-1}[BH^+] \tag{31}$$

i.e., the rate of reaction of the ion with bromine $k_2[Br_2][I]$ is much greater than the rate $k_{-1}[BH^+][I]$ at which it reverts to acetone, or an overwhelming proportion of the ions formed by reaction of acetone with base are converted to bromacetone. Under these conditions the denominator on the right of equation (30) reduces to $k_2[Br_2]$, which cancels with the numerator and leads to

$$-\frac{d[K]}{dt} = \frac{d[Y]}{dt} = k_1[K][B] \tag{32}$$

The rate of reaction is the rate of the first step [reaction (II)]; in agreement with experiment it is proportional to the product of the concentrations of acetone and base and independent of the concentration of bromine. The detailed analysis leads, therefore, to the same result as the qualitative one.

When the opposite extreme applies, *viz.*,

$$k_2[Br_2] \ll k_{-1}[BH^+] \tag{33}$$

equation (30) reduces to

$$-\frac{d[K]}{dt} = \frac{d[Y]}{dt} = k_2\frac{k_1}{k_{-1}}\frac{[K][B]}{[BH^+]}[Br_2] \qquad (34)$$

But by the application of the law of equilibrium together with the relation (22) to reaction (II) the concentration of the ion I is

$$[I]_e = \frac{k_1}{k_{-1}}\frac{[K][B]}{[BH^+]} \qquad (35)$$

if a state of equilibrium exists with respect to this reaction. Consequently, equation (34) reduces to

$$-\frac{d[K]}{dt} = \frac{d[Y]}{dt} = k_2[I]_e[Br_2] \qquad (36)$$

and the rate of reaction is that of the second step [reaction (III)] with the concentration [I] determined by an approximately equilibrium status of the first step.

When neither the approximation of equation (31) nor that of (33) may be applied, the general equation (30) applies and the reaction shows no simple order with respect to any of the reactants except acetone and base. This situation has been observed in the base-catalyzed chlorination of acetone[2] and in the iodination of acetophenone in moderately concentrated aqueous sulfuric acid (page 231).

The Christiansen Formulation.[6b,8]—If in the system of reac-

$$\left. \begin{array}{l} A + B \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} X_1 + C \\[4pt] X_1 + D \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} X_2 + E \\[4pt] X_2 + F \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} X_3 + G \\[4pt] \quad \cdot \ \cdot \ \cdot \ \cdot \ \cdot \ \cdot \ \cdot \\[4pt] X_{(n-1)} + L \underset{k_{-n}}{\overset{k_n}{\rightleftharpoons}} M + N \end{array} \right\} \qquad (V)$$
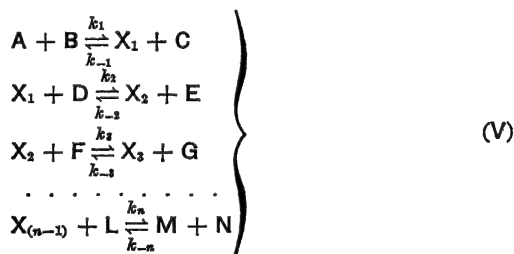
tions (V) substances X_1, X_2, etc., are unstable intermediates to which the approximation of the last section may be applied, a very elegant formulation is possible. A set of quantities w are

[8] CHRISTIANSEN, *Z. physik. Chem.*, **33B**, 145 (1936); **37B**, 374 (1937).

defined such that the rate of each step divided by the concentration of the unstable intermediate involved is given by one of them; thus

$$\left.\begin{aligned}
w_1 &= v_1 = k_1[A][B] \\
w_{-1} &= \frac{v_{-1}}{[X_1]} = k_{-1}[C] \\
w_2 &= \frac{v_2}{[X_1]} = k_2[D] \\
w_{-2} &= \frac{v_{-2}}{[X_2]} = k_{-2}[E]
\end{aligned}\right\} \tag{37}$$

etc.

The total rate v of the conversion of A and B to M and N is, in view of the unstable intermediate situation, equal to the rate of each of the steps, there being no storage in the form of any of the X's. Hence,

$$v = w_1 - w_{-1}[X_1] = w_2[X_1] - w_{-2}[X_2] = w_3[X_2] - w_{-3}[X] = \text{etc.}$$

The solution of this set of n simultaneous equations involving v and the $n - 1[X]$'s is obtainable by the method of determinants and may be expressed in the form

$$v = v_+ - v_- \tag{38}$$

with

$$\frac{1}{v_+} = \frac{1}{w_1} + \frac{w_{-1}}{w_1 w_2} + \frac{w_{-1} w_{-2}}{w_1 w_2 w_3} + \cdots \frac{w_{-1} w_{-2} \cdots w_{-(n-1)}}{w_1 w_2 w_3 \cdots w_n} \tag{39}$$

and

$$\frac{1}{v_-} = \frac{1}{w_{-n}} + \frac{w_n}{w_{-n} w_{-(n-1)}} + \cdots \frac{w_n w_{n-1} \cdots w_2}{w_{-n} w_{-(n-1)} \cdots w_{-1}} \tag{40}$$

An important feature of this result is the fact that the rate may always be expressed as the difference between the rates of a forward and of a reverse reaction.

Applied to the acetone halogenation, equations (37) to (40) take the form

$$w_1 = k_1[K][B]$$
$$w_{-1} = k_{-1}[BH^+]$$
$$w_2 = k_2[Br_2]$$
$$w_{-2} = 0$$

which substituted in equation (39) leads to

$$\frac{1}{v_+} = \frac{1}{k_1[\mathrm{K}][\mathrm{B}]} + \frac{k_{-1}[\mathrm{BH}^+]}{k_1[\mathrm{K}][\mathrm{B}]k_2[\mathrm{Br}_2]} = \frac{k_2[\mathrm{Br}_2] + k_{-1}[\mathrm{BH}^+]}{k_1k_2[\mathrm{K}][\mathrm{B}][\mathrm{Br}_2]} \quad (41)$$

which is identical with equation (30). Equation (40) leads to

$$\frac{1}{v_-} = \frac{1}{0} + \frac{1}{0} \qquad \text{or} \qquad v_- = 0$$

A further advantage of this formulation is the aid that it offers in the integration of the rate equation for an irreversible reaction. Equation (39) or (40) expresses the reciprocal rate dt/dx as the sum of a series of terms, which may be written as functions of x of a type that may always be integrated by the method of partial fractions.

The Racemization of an Optically Active Ketone.—This consists in the reversible conversion of one enantiomorph to the other by way of the ion. By using dK and lK to represent dextro- and levo-rotatory ketone, the reactions are

$$d\mathrm{K} + \mathrm{B} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{I} + \mathrm{BH}^+ \qquad \text{(VI)}$$

$$\mathrm{I} + \mathrm{BH}^+ \underset{k_1}{\overset{k_{-1}}{\rightleftharpoons}} l\mathrm{K} + \mathrm{B} \qquad \text{(VII)}$$

The use of the same constants k_1 and k_{-1} in the two steps is a necessary result of the properties of enantiomorphs. The application of the Christiansen equations leads to

$$\frac{1}{v_+} = \frac{1}{k_1[d\mathrm{K}][\mathrm{B}]} + \frac{k_{-1}[\mathrm{BH}^+]}{k_1[d\mathrm{K}][\mathrm{B}]k_{-1}[\mathrm{BH}^+]}$$

hence,

$$v_+ = \frac{1}{2}k_1[d\mathrm{K}][\mathrm{B}]$$

Similarly,

$$v_- = \frac{1}{2}k_1[l\mathrm{K}][\mathrm{B}]$$

and

$$v = -\frac{\mathrm{d}[d\mathrm{K}]}{\mathrm{d}t} = \frac{\mathrm{d}[l\mathrm{K}]}{\mathrm{d}t} = \frac{1}{2}k_1[\mathrm{B}]\{[d\mathrm{K}] - [l\mathrm{K}]\} \qquad (42)$$

The experimental quantity is the value of the rotation α which

is proportional to the difference in the concentrations of the enantiomorphs

$$\alpha = m\{[d\text{K}] - [l\text{K}]\} \tag{43}$$

By virtue of this and the derivative

$$\frac{d\alpha}{dt} = m\left\{\frac{d[d\text{K}]}{dt} - \frac{d[l\text{K}]}{dt}\right\} = \frac{-2m\,d[l\text{K}]}{dt} \tag{44}$$

equation (42) becomes

$$\frac{d\alpha}{dt} = k_1[\text{B}]\alpha \tag{45}$$

or

$$\ln \alpha_0 - \ln \alpha = k_1[\text{B}]t \tag{46}$$

The constant obtained by the usual first-order plot of $\log \alpha$ against t is, therefore, k_1, the specific rate in the forward direction of reaction (VI). By equations (II) and (32) it is identical with the specific rate of the halogenation.

Deuterium Exchange in Ketones.—The reactions of the deuterium exchange are (HI represents protium ketone, DI deuterium ketone)

$$\text{HI} + \text{B} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \text{I}^- + \text{BH}^+ \qquad\qquad \text{VIII}$$

$$\text{I}^- + \text{BD}^+ \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} \text{DI} + \text{B} \qquad\qquad \text{IX}$$

By equations (38) to (40)

$$\frac{d[\text{DI}]}{dt} = \frac{k_1 k_2[\text{HI}][\text{B}][\text{BD}^+] - k_{-1}k_{-2}[\text{DI}][\text{B}][\text{BH}^+]}{k_{-1}[\text{BH}^+] + k_2[\text{BD}^+]} \tag{47}$$

When protium ketone is dissolved in deuterium water, the concentration of BD^+ is much greater than that of BH^+. Since, furthermore, the constants k_{-1} and k_2 do not differ by a large factor (estimates of the ratio k_{-1}/k_2 in various reactions vary from 3 to 10),[9] the denominator reduces to $k_2[\text{BD}^+]$. By the same token, since $k_1 k_2$ and $k_{-1}k_{-2}$ are of the same order of magnitude, the numerator reduces to $k_1 k_2[\text{HI}][\text{B}][\text{BD}^+]$ especially at the beginning of the reaction when $[\text{DI}] < [\text{HI}]$. Consequently, equation (47) reduces to

$$\frac{d[\text{DI}]}{dt} = k_1[\text{HI}][\text{B}] \tag{48}$$

[9] Bonhoeffer, *Trans. Faraday Soc.*, **34**, 252 (1938).

for the initial rate of reaction of protium ketone in pure deuterium water, and the specific rate of the deuterium uptake is identical with that of halogenation and racemization. The small difference observed experimentally (page 98) in 99 per cent D_2O is accounted for[4] if $k_{-1}/k_2 = 12$.

Energy of Activation.—It was first observed by Arrhenius that a plot of the logarithm of the rate constant against the reciprocal of the absolute temperature is to a considerable precision a straight line. Hence,

$$\log k = \frac{a}{T} + b \tag{49}$$

or

$$\frac{d(\ln k)}{dT} = -\frac{2.303a}{T^2} \tag{50}$$

This equation is immediately reminiscent of the equation [(25), Chap. III] for the variation of equilibrium constant with temperature. If equation (50) is put in a similar form

$$\frac{d(\ln k)}{dT} = \frac{E^a}{RT^2} \tag{51}$$

the quantity E^a is called the *energy of activation* of the reaction and is defined explicitly by

$$E^a = \frac{RT^2 d(\ln k)}{dT} \tag{52}$$

The energies of activation of a forward reaction E_1^a and of its reverse reaction E_{-1}^a are necessarily related to the heat of the reaction ΔH. From equation (22)

$$\ln K = \ln k_1 - \ln k_{-1}$$

hence,

$$\frac{RT^2 d(\ln K)}{dT} = \frac{RT^2 d(\ln k_1)}{dT} - \frac{RT^2 d(\ln k_{-1})}{dT} \tag{53}$$

By equation (52) and equation (25), Chap. III, this becomes

$$\Delta H = E_1^a - E_{-1}^a \tag{54}$$

Since ΔH varies with temperature [equation (27), Chap. III], the

apparent constancy of the energy of activation is illusory[10] and depends upon the fact that the range of temperatures over which it may be measured is limited. If one attempts to proceed to higher temperatures, the reaction rate becomes too fast for accurate measurement, at lower temperatures it is too slow. In those cases in which ΔH is most largely dependent on the temperature, *viz.*, in reactions involving ions, it has, however, been shown beyond question that the energy of activation is also a function of temperature.[10a,11]

The Collision Theory.—There have been two important theoretical approaches to the interpretation of the phenomena of reaction kinetics. Both have their usefulness and their weakness. The earlier in point of development, the collision theory, starts out from the consideration of the frequency of collisions between the reacting molecules. Obviously, molecules can react only when they come in contact, *i.e.*, collide with each other. Gas kinetic theory gives for Z, the frequency of collision between the spherical molecules of the substances A and B, the diameters of which are σ_A and σ_B and the masses of which are m_A and m_B, the value

$$Z = N_A N_B \left(\frac{\sigma_A + \sigma_B}{2}\right)^2 \sqrt{8\pi k T\left(\frac{1}{m_A} + \frac{1}{m_B}\right)} \qquad (55)$$

where N_A and N_B are the numbers of molecules of each kind per cubic centimeter. The collision frequency would probably not be very different for irregularly shaped molecules, but a serious complication arises from the fact that reaction can result only if the proper parts of the molecules come in contact. In the reaction of sodium atoms with methyl iodide, which leads to sodium iodide and methyl radicals (page 144), the collision of a sodium atom with the methyl end of a methyl iodide molecule cannot possibly lead to reaction, the sodium must collide with the iodine. In the reaction with phenyl or amyl halide an even smaller fraction of the surface of the halide is available for reaction. It must, therefore, be expected that the frequency of collisions between

[10] (a) TRAUTZ, *Z. anorg. allgem. Chem.*, **102**, 81 (1918). (b) SCHEFFER and BRANDSMA, *Rec. trav. chim.*, **45**, 522 (1926). (c) LaMER, *J. Chem. Phys.*, **1**, 289 (1933).

[11] LaMER and MILLER, *J. Am. Chem. Soc.*, **57**, 2674 (1935). MOELWYN-HUGHES, *Proc. Roy. Soc.* (London), **164**, 295 (1938).

complex organic molecules which can possibly lead to reaction will be smaller and possibly many times smaller than that given by equation (55).

The theory does give the observed dependence of rate upon concentration (through the factor $N_A N_B$) if it is admitted that a constant fraction of the collisions results in reaction. This fraction is, however, a very small number and one dependent on temperature in the case of those reactions the rates of which are easily measured. The temperature dependence follows from logarithmic differentiation of equation (55) with respect to temperature, which yields

$$\frac{\mathrm{d}\ln Z}{\mathrm{d}T} = \frac{1}{2T} \tag{56}$$

Hence the logarithm of the collision frequency varies at the same rate for all reactions, the change in Z amounting to 0.16 per cent per degree at room temperature. The experimental variation in reaction rate for reactions that are neither too fast nor too slow for measurement is, however, of the order of 10 per cent per degree, and the ratio k/Z is a rapidly increasing function of temperature.

The collision theory assumes that the effective collisions are those in which an especially large amount of energy is available. This might mean that one or both of the reacting molecules possess a large amount of internal energy or that one or both are moving so rapidly that the collision is an especially violent one. In either case it is assumed that the fraction of collisions of sufficient energy is given by

$$e^{-\epsilon/kT} = e^{-E/RT}$$

which is obviously a Boltzmann sort of expression. Its exact applicability to the problem in question is not entirely clear, and this uncertainty lies at the root of most of the weakness of the collision theory. It is an exact expression for the fraction of collisions in which the component of translational energy along the line of centers exceeds the value ϵ, *i.e.*, of those for which the intensity of the collision exceeds a definite minimum; it is approximately the expression for the fraction in which the energy resident in any degree of freedom exceeds the same minimum.

In so far as it is correct, the number of molecules reacting per second is

$$-\frac{dN_A}{dT} = N_A N_B \left(\frac{\sigma_A + \sigma_B}{2}\right)^2 \sqrt{8\pi kT\left(\frac{1}{m_A} + \frac{1}{m_B}\right)} e^{-E/RT} \quad (57)$$

and the rate constant is, since $N = cN/1000$,

$$k = \frac{N}{1000}\left(\frac{\sigma_A + \sigma_B}{2}\right)^2 \sqrt{8\pi kT\left(\frac{1}{m_A} + \frac{1}{m_B}\right)} e^{-E/RT} \quad (58)$$

Logarithmic differentiation now leads to

$$\frac{d \ln k}{dT} = \frac{1}{2T} + \frac{E}{RT^2} \quad (59)$$

hence the energy of activation [equation (52)] is

$$E^a = E + \frac{1}{2}RT \quad (60)$$

In most cases the quantity $\frac{1}{2}RT$ is so small that it may be neglected, and E becomes equal to the experimentally determined energy of activation.

The theory may be tested by measuring the temperature coefficient of the reaction rate, obtaining the energy of activation by equation (52), and substituting this for E in equation (57). If reasonable values for the molecular diameters then lead to a correct value for the rate of reaction, the theory is verified. The earliest studies, made on relatively simple reactions in the gas phase, were on the whole satisfactory, *i.e.*, the calculated and experimental rates agree within an order of magnitude or so.[12] In view of the uncertainty implicit in the use of equation (55) for irregularly shaped molecules, only part of whose surface is available for reaction, the result is not unsatisfactory. More recent work[13] on the reactions of complex molecules, such as the Diels-Alder reaction of cyclopentadiene with acrolein, has shown that, even in gas reactions, rates calculated from the collision

[12] HINSHELWOOD, "The Kinetics of Chemical Change in Gaseous Systems," Oxford, 1933.

[13] (a) KISTIAKOWSKI and LACHER, *J. Am. Chem. Soc.*, **58**, 123 (1936). (b) WASSERMANN, *Trans. Faraday Soc.*, **34**, 128 (1938).

theory may differ from the experimental value by a factor of 100,000. For reactions in solution the difficulties of the theory are still more serious. Although the rate predicted by the collision theory may be considered the most probable value, discrepancies as large as a factor of 10^6 are not uncommon.[14] As a consequence, it has become customary in collision-theory discussions to write the rate constant k as

$$k = PZ^{\circ}e^{-E_a/RT} \tag{61}$$

Z° is the frequency of collisions at unit concentration of all reactants, and is generally close to 3×10^{11} l./mole sec., and P is a *probability factor* that represents the discrepancy between collision theory and experiment.

The difficulties of the collision theory which arise from the use of the simple exponential factor in equation (57) or (58) are similar to those which appear in the theory of equilibrium when the attempt is made to identify a temperature dependent heat of reaction ΔH with the temperature-independent potential-energy change ΔE_P (page 77). Indeed the analysis that was applied to the equilibrium case is pertinent here also. There must be not one kind of a system of A and B molecules in the act of collision but a series each with its characteristic internal energy determined by quantum laws and with its probability determined by an expression of the type $pe^{-\epsilon/kT}$ in which ϵ is the energy of the state. Consequently, the rate of reaction must be proportional to the sum of the rates corresponding to each of these states[10e]

$$k = k_0 p_0 e^{-\epsilon_0/kT} + k_1 p_1 e^{-\epsilon_1/kT} + k_2 p_2 e^{-\epsilon_2/kT} + \cdots \tag{62}$$

As in the equilibrium problem, logarithmic differentiation does not give a value of $RT^2 \dfrac{\mathrm{d}\ln k}{\mathrm{d}T}$ which is equal to any one of the $N\epsilon_i$ values or to their average or which is even independent of temperature. Indeed, the equation is too complicated to lead to any verifiable or useful results.

The Transition-state Theory.—The alternative treatment of the reaction-rate problem, usually called the *transition-state*

[14] MOELWYN-HUGHES, "The Kinetics of Reactions in Solutions," Oxford, 1933.

theory, shares with the collision theory the idea of an energy of activation. Indeed this idea predominates to such an extent that the theory does not explicitly consider the molecular collisions which form a coordinate feature of the collision theory and which must in fact be a necessary part of the process of reaction. Both theories are abstractions of a sort that are frequently necessary in the development of science; whereas the collision theory has oversimplified the concept of activation, the other glosses over the necessity of collision.

The theory starts from the idea that a molecule or group of molecules can react only if it gets into a state in which it contains much more than the usual amount of energy. It must, according to a frequently used phrase, cross an energy hill or barrier. Just as a hill has a summit from which it is possible without further expenditure of energy to roll down on either side, so a reacting system must go through a state, the transition state, from which it may advance to form the reaction products or return to form the reactants, without in either case requiring any further supply of energy. The transition state is the half-reacted state; in view of its high energy content and in the light of the Boltzmann principle it must be a relatively improbable state, one in which only a small fraction of the molecules exist at any time.

The transition-state theory[15] endows this transition state with many of the properties of a stable substance. The justification for this is most easily visualized in terms of the following considerations.[15c] If the reversible reaction

$$A \rightleftharpoons B \qquad \qquad (X)$$

is in a state of equilibrium so that A is being converted to B and B to A at equal rates, there must also be equilibrium with respect to all the intermediate states between A and B. In particular, there must be equilibrium between the molecules of the reactant and those in the transition state, so that the concentration of molecules in that state $C^{\ddagger}$ is related to the concentration of A by the equilibrium equation

$$\frac{C^{\ddagger}}{C_A} = K^{\ddagger} \qquad \qquad (63)$$

[15] (a) Pelzer and Wigner, *Z. physik. Chem.*, **B15**, 445 (1932). (b) Eyring, *J. Chem. Phys.*, **3**, 107 (1935). (c) Evans and Polanyi, *Trans. Faraday Soc.*, **31**, 875 (1935).

Since $K^{\ddagger}$ is an equilibrium constant, it must satisfy the fundamental equations for an equilibrium state (page 77) in the form

$$\Delta G^{\ddagger} \equiv -RT \ln K^{\ddagger} = \Delta E_P^{\ddagger} + \Delta E_z^{\ddagger} - RT \ln \frac{f^{\ddagger}}{f_A} \quad (64)$$

$$\Delta H^{\ddagger} \equiv RT^2 \frac{d \ln K^{\ddagger}}{dT} = \Delta E_P^{\ddagger} + \Delta E_z^{\ddagger} + RT^2 \frac{d \ln (f^{\ddagger}/f_A)}{dT} \quad (65)$$

Here $f^{\ddagger}$ is the partition function for the transition state, and $\Delta G^{\ddagger}$ and $\Delta H^{\ddagger}$ are called the free energy and the heat of activation, respectively.

Because the rates of the forward and reverse reactions are equal, just half of the molecules in the transition state must be in the process of reacting to form B, the other half in the process of reacting to form A. The rate of conversion of A to B is, therefore, $\frac{1}{2}v^{\ddagger}K^{\ddagger}c_A$, for $K^{\ddagger}c_A$ is the concentration of molecules in the transition state, $v^{\ddagger}$ is their specific reaction rate, and one-half of them are reacting in this direction. But the concentration of molecules that are in the course of reacting from B to A can have no influence upon the concentration of those reacting from A to B. Consequently, the rate of the latter process must remain the same, even though the system is no longer in equilibrium, when the former reaction is suppressed by reducing the concentration of B to a very low value. The specific rate of the A $\rightarrow$ B reaction is, therefore,

$$k = \frac{1}{2}v^{\ddagger}K^{\ddagger} \quad (66)$$

regardless of the extent to which the reverse reaction may be occurring. The transition-state theory now proposes the hypothesis that the quantity $\frac{1}{2}v^{\ddagger}$ has the same value for all reactions and that, in particular, it is equal to kT/h.[15b] This hypothesis is an eminently reasonable one in terms of general statistical mechanical considerations. It is strongly supported by the usefulness of its corollary that the change in rate of reaction produced by a change in the structure of a reactant or in the medium in which the reaction occurs is proportional to the change in a quantity that has the properties of an equilibrium constant.[16] Thus if k_a is the rate constant for the reaction of a particular

[16] WYNNE-JONES and EYRING, *J. Chem. Phys.*, **3**, 492 (1935).

substance in a particular medium and k_b is the constant for another reactant or for the same reactant in another medium, then

$$\frac{k_a}{k_b} = \frac{K_a^{\ddagger}}{K_b^{\ddagger}} \qquad \cdot \qquad (67)$$

where the K's are equilibrium constants, subject to equations (64) and (65).

Potential Energies and Kinetic Energies in the Reaction-rate Problem.—In view of the definitions given in equations (64) and (65) and the constancy of $v^{\ddagger}$, the difference in free energies of activation of two reactions is given by

$$\begin{aligned}
\Delta G_a^{\ddagger} - \Delta G_b^{\ddagger} &= -RT \ln \frac{k_a}{k_b} \\
&= (\Delta E_{Pa}^{\ddagger} - \Delta E_{Pb}^{\ddagger}) + (\Delta E_{za}^{\ddagger} - \Delta E_{zb}^{\ddagger}) - \\
&\qquad\qquad RT \ln \frac{f_a^{\ddagger} f_b}{f_b^{\ddagger} f_a} \quad (68)
\end{aligned}$$

and the difference in the heats of activation by

$$\begin{aligned}
\Delta H_a^{\ddagger} - \Delta H_b^{\ddagger} &= RT^2 \frac{d \ln \dfrac{k_a}{k_b}}{dT} \\
&= (\Delta E_{Pa}^{\ddagger} - \Delta E_{Pb}^{\ddagger}) + (\Delta E_{za}^{\ddagger} - \Delta E_{zb}^{\ddagger}) + \\
&\qquad\qquad RT^2 \frac{d}{dT}\left(\ln \frac{f_a^{\ddagger} f_b}{f_b^{\ddagger} f_a} \right) \quad (69)
\end{aligned}$$

As in the equilibrium case (page 77) the problem of the effect of structure upon rate of reaction and upon its temperature coefficient reduces to the consideration of the sum of two terms, one of which depends upon potential energies only, whereas the other requires a knowledge of the kinetic energies of vibration and rotation.

Here also the case that

$$\Delta G_a^{\ddagger} - \Delta G_b^{\ddagger} = \Delta H_a^{\ddagger} - \Delta H_b^{\ddagger} \qquad (70)$$

is an important special one, which can occur only if the terms involving the f's in equations (68) and (69) vanish, which implies a large probability that the term involving the E_z's also vanishes. Consequently, in this case but in this case only, the quantity

$-RT \ln \dfrac{k_a}{k_b}$ measures the difference in the potential energies of activation of the two reactions $\Delta E_{Pa}{}^{\ddagger} - \Delta E_{Pb}{}^{\ddagger}$. Only in this case can either $-RT \ln \dfrac{k_a}{k_b}$ or the change in heat of activation $\Delta H_a{}^{\ddagger} - \Delta H_b{}^{\ddagger}$ be interpreted in terms of electron displacements, dipole fields, or the like.

By analogy with thermodynamic quantities an entropy of activation $\Delta S^{\ddagger}$ may be defined by the equation

$$\Delta S^{\ddagger} = \frac{\Delta H^{\ddagger} - \Delta G^{\ddagger}}{T} \tag{71}$$

Like the thermodynamic entropy it may be expressed as a function of $\Delta G^{\ddagger}$ alone by combining the defining equations for $\Delta H^{\ddagger}$ and $\Delta G^{\ddagger}$ [(64) and (65)] to give

$$\Delta H^{\ddagger} = -T^2 \frac{d\left(\dfrac{\Delta G^{\ddagger}}{T}\right)}{dT} = -T^2 \frac{\dfrac{T d\Delta G^{\ddagger}}{dT} - \Delta G^{\ddagger}}{T^2}$$

$$T\Delta S^{\ddagger} = \Delta H^{\ddagger} - \Delta G^{\ddagger} = -\frac{T d\Delta G^{\ddagger}}{dT}$$

and

$$\Delta S^{\ddagger} = -\frac{d\Delta G^{\ddagger}}{dT} \tag{72}$$

The condition of equation (70) which permits the interpretation of the effect of structure on reaction rate in terms of potential-energy quantities may by equation (71) be expressed as

$$\Delta S_a{}^{\ddagger} - \Delta S_b{}^{\ddagger} = 0 \tag{73}$$

The condition is, therefore, that the entropies of activation have the same value for the different reactants. In view of equation (72) and the definition of $G^{\ddagger}$ it may be expressed as

$$\frac{d\left(RT \ln \dfrac{k_a}{k_b}\right)}{dT} = 0 \tag{74}$$

in which form its applicability may be most easily tested.

The same condition may be expressed in terms of the probability factor P of the collision theory by the following considerations. The quantity P is defined by equation (61), which together with the definition of the energy of activation (52) leads to

$$\ln P = \ln k - \ln Z + T \frac{\mathrm{d} \ln k}{\mathrm{d} T}$$

and for two reactions a and b

$$\ln \frac{P_a}{P_b} = \ln \frac{k_a}{k_b} - \ln \frac{Z_a}{Z_b} + T \frac{\mathrm{d} \ln \frac{k_a}{k_b}}{\mathrm{d} T} \tag{75}$$

whereas the same considerations that led to equation (74) show that

$$\Delta S_a^{\ddagger} - \Delta S_b^{\ddagger} = \frac{\mathrm{d}\left(RT \ln \frac{k_a}{k_b} \right)}{\mathrm{d} T} = R \ln \frac{k_a}{k_b} + RT \frac{\mathrm{d} \ln \frac{k_a}{k_b}}{\mathrm{d} T} \tag{76}$$

Equations (75) and (76) are consistent only if

$$\Delta S_a^{\ddagger} - \Delta S_b^{\ddagger} = R \ln \frac{P_a Z_a}{P_b Z_b} \tag{77}$$

The condition of equations (70), (73), and (74) may, therefore, be put in the form that the PZ product must have the same value for the reactions compared. Since the Z factor is not likely to differ greatly, this is practically equivalent to the condition that P have the same value for the different reactions.

The determination of energy of activation and probability factor, useful and important as these data are, does not represent an analysis of the rate problem into simpler terms. The only helpful analysis is into potential and kinetic energies, and the energy of activation $\Delta H^{\ddagger}$ is no more reliable a measure of the potential-energy quantity $\Delta E_P^{\ddagger}$ than is the free energy of activation or $-RT \ln k$. Only in so far as it determines whether the simplifying condition of equations (70), (73), and (74) applies does the determination of the activation energy yield any closer approach to the problem of structure and reactivity than does the measurement of the rate constant at one temperature.

Reaction Series with Constant Entropies of Activation: Benzene Derivatives.—In close analogy with the equilibrium problem the entropy of activation has been found to be constant in any series of reactions in which the members of the series differ only by a meta or para substituent in a benzene derivative. Thus Table I lists the specific rates at 25°c of the saponification by sodium hydroxide in 85 per cent ethanol-water solution of a series of ethyl esters of carboxylic acids and the difference between the entropy of activation $\Delta S^{\ddagger}$ of each ester and that of ethyl benzoate $\Delta S_0^{\ddagger}$.

TABLE I.—ALKALINE HYDROLYSIS OF ETHYL ESTERS IN 85 PER CENT
ETHANOL

Rate constants (liters per mole sec.) at 25°c and relative entropies of activation (calories per degree). Reference substance ethyl benzoate[17]

Ester	$10^4 k$	$\Delta S^{\ddagger} - \Delta S_0^{\ddagger}$	Ester	$10^4 k$	$\Delta S^{\ddagger} - \Delta S_0^{\ddagger}$
Benzoic[17a]	5.50	0	o-Chlor benzoic	13.9	−4.7
p-Amino benzoic	0.127	−0.1	o-Nitro benzoic	54.1	−4.5
p-Methoxy benzoic	1.15	−0.3	Acetic	69.5	−5.1
p-Methyl benzoic	2.51	+0.1	Propionic	35.5	−6.6
p-Chlor benzoic	23.7	−0.3	n-Butyric	18.3	−6.3
p-Brom benzoic	28 9	0.0	i-Butyric	8.01	−8.5
p-Iodo benzoic	27.8	−0 1	n-Valeric	19 2	−7.4
p-Nitro benzoic	567.	−1.8	i-Valeric	4.27	−7.3
Benzoic[17b]	6.21	+0.1	Methylethylacetic	3.08	−8.5
m-Methyl benzoic	4.33	−0.2	Trimethylacetic	0.254	−8.1
m-Chlor benzoic	47.7	−1.0	n-Hexoic	20.7	−7.0
m-Nitro benzoic	429.	+0 8	Diethylacetic	0.157	−8.1
p-Fluo benzoic	12.6	−0.1	n-Heptoic	17.9	−6.9
p-Nitro benzoic	720.	−0.2	n-Octoic	18.4	−6.4
o-Methyl benzoic	0.776	−3.3			
o-Fluo benzoic	23.2	−0.2			

The mean value of the entropy difference for the meta and para derivatives is −0.2, and the median deviation of the individual values from the mean, the "probable error of a value,"[18]

[17] (a) Data for the first 8 items from Ingold and Nathan, *J. Chem. Soc.*, 222 (1936). (b) Remaining data from Evans, Gordon, and Watson, *J. Chem. Soc.*, 1430 (1937); 1439 (1938); the data for acetate, propionate, and butyrate corrected by Smith and Levenson, *J. Am. Chem. Soc.*, **61**, 1173 (1939).

[18] WRIGHT and HAYFORD, "The Adjustment of Observations," New York, 1906.

is 0.3. This is no greater than the experimental uncertainty since a probable error of 1 per cent in k leads to a probable error in $\Delta S^{\ddagger}$ of 0.34. Furthermore, the largest changes in $\Delta S^{\ddagger}$ appear in those cases where the rate is so fast that its precise measurement is difficult.

The constancy in entropy of activation is confined to the meta and para derivatives. With the notable exception of the fluorine compound, the entropies of activation are lower for the ortho derivatives by an amount well over the experimental error. The values for the aliphatic esters are still lower, the difference between benzoic and aliphatic esters being equivalent to nearly two orders of magnitude in the value of k.

The relatively small effect of a meta or para substituent upon entropy of activation is a phenomenon of considerable generality. The median deviation of the values of $\Delta S^{\ddagger}$ for the reaction of para and meta substituted anilines with similarly substituted benzoyl chlorides[19] is 0.9; for the alcoholysis of eight para and meta substituted triphenylmethyl chlorides,[20] 1.05; for the alkaline hydrolysis of five benzyl acetates,[21] 0.06; for the alkaline hydrolysis of eight phenyl acetates,[21] 0.3; for the alkaline hydrolysis of seven ethyl benzoates in acetone-water solution,[21] 0.5; for the acid hydrolysis of six phenyl acetates,[21] 0.6; for the acid hydrolysis of five benzyl acetates,[21] 0.3; for the methylation of seven para substituted dimethylanilines,[22a] 0.6; for the acid-catalyzed esterification of nine benzoic acids, 1.1;[22b] for the acid hydrolysis of eight ethyl benzoates,[23] 1.5 in alcohol-water and 0.5 in acetone-water solution.

It has been suggested[23,24] that in some reactions $\Delta S^{\ddagger}$ or, what is the same thing, $\log P$ may vary as a function of $\Delta G^{\ddagger}$ or of $\Delta H^{\ddagger}$. As in the equilibrium case (page 84) such a relation is entirely reasonable for reactions involving ions or leading to the formation of ions. Whether it really exists does not appear from the

[19] WILLIAMS and HINSHELWOOD, *J. Chem. Soc.*, 1079 (1934).

[20] NIXON and BRANCH, *J. Am. Chem. Soc.*, **58**, 492 (1936).

[21] TOMMILA and HINSHELWOOD, *J. Chem. Soc.*, 1801 (1938).

[22] (a) DAVIES, *J. Chem. Soc.*, 1865 (1938). (b) HARTMAN and BORDERS, *J. Am. Chem. Soc.*, **59**, 2107 (1937).

[23] TIMM and HINSHELWOOD, *J. Chem. Soc.*, 862 (1938).

[24] HAMMETT, *J. Chem. Phys.*, **4**, 613 (1936); *J. Am. Chem. Soc.*, **59**, 96 (1937). HINSHELWOOD, LAIDLER, and TIMM, *J. Chem. Soc.*, 848 (1938).

available data. *Thus the data[25] for the alkaline hydrolysis of eight para and meta substituted derivatives of $C_6H_5OSO_3^-$ can be fitted to the equation $\Delta S^{\ddagger} = a + b\Delta G^{\ddagger}$. The best value of the slope b is found by least squares methods to be 0.0044 with a probable error of 0.003. This leaves little assurance that the variations in $\Delta S^{\ddagger}$ are anything but random.

Relations between $\Delta S^{\ddagger}$ and $\Delta H^{\ddagger}$ or between log PZ and E^a are especially likely to be illusory in cases in which the variation in rate constant from substance to substance is small. If k were constant and $\Delta H^{\ddagger}$ variable, log PZ would necessarily be linear in $\Delta H^{\ddagger}$ with the slope $1/(2.303RT)$.

In the light of this evidence and that obtained from the study of equilibrium (page 84), it is clear that *the effect of a para or meta substituent on the reactions of benzene derivatives is exerted solely or chiefly through the ΔE_P term of equation* (64) *and equation* (30), *Chap. III*. The substituent has little or no effect upon the terms that involve the internal kinetic energies. Consequently, such reactions offer an especially simple case in the general problem of the effect of structure upon reactivity (page 118).

On the other hand, it is quite as apparent that other kinds of change in structure are likely to involve both the kinetic and the potential-energy terms of the fundamental equilibrium and kinetic equations. The evidence to this effect in Table I is supported by the following. The entropy of activation for the acid hydrolysis of ethyl trichloracetate is 11.8 cal./deg. less than for ethyl acetate, and the value for the latter is 1.5 units higher than the average for the meta and para substituted benzoic esters.[23] It averages 4.6 units less for the reaction of alkyl iodides with triethylamine than for their reaction with pyridine.[26] It is 11.8 units greater for the acid-catalyzed esterification in methanol of benzoic than for that of diphenylacetic acid.[27] Finally, the wide variations in the entropies of ionization of carboxylic acids (page 84), together with the Brønsted law (page 222) connecting ionization constants with rate constants

[25] BURKHARDT, HORREX, and JENKINS, *J. Chem. Soc.*, 1649 (1936).

[26] LAIDLER and HINSHELWOOD, *J. Chem. Soc.*, 858 (1938).

[27] HINSHELWOOD and LEGARD, *J. Chem. Soc.*, 587 (1935). SMITH, *J. Am. Chem. Soc.*, **61**, 254 (1939).

of catalyzed reactions, require a considerable variability in the entropies of activation of the catalyzed reactions. The available data[23] are consistent with this requirement.[23]

There are, however, cases in which ortho substituents have a negligible effect upon the entropy of activation. In the hydrolysis of aryl sulfuric acids,[25] ortho substituted derivatives show a slightly smaller median deviation (1.0 cal./deg.) than the meta and para compounds (1.2) from the equation defined by the latter (page 123).

Temperature Effects in Orientation in the Benzene Ring.—A reaction involving substitution in the benzene ring usually occurs in more than one position relative to an existing substituent and would no doubt be found to take place in all possible positions were sufficiently sensitive methods of analysis of the reaction product available. If a monosubstituted benzene C_6H_5A reacts with the substance RB to form the various compounds C_6H_4AB, the rate of formation of the para derivative will be given by some such equation as

$$\frac{d[p-C_6H_4AB]}{dt} = k_p[C_6H_5A]^x[RB]^y \qquad (78)$$

and that of the ortho derivative by

$$\frac{d[o-C_6H_4AB]}{dt} = 2k_o[C_6H_5A]^x[RB]^y \qquad (79)$$

Here k_p and k_o are the specific rates of reaction of RB with a para and with an ortho carbon atom, and the statistical factor 2 in equation (79) arises from the fact that there are two ortho positions. If, as is probable, the factors x and y are the same, division of equation (79) by equation (78) yields

$$\frac{d[o-C_6H_4AB]}{d[p-C_6H_4AB]} = \frac{2k_o}{k_p} \qquad (80)$$

which may be integrated immediately to

$$\frac{[o-C_6H_4AB]}{[p-C_6H_4AB]} = \frac{2k_o}{k_p} \qquad (81)$$

[23] SMITH, *J. Chem. Soc.*, 1744 (1934). BAUGHAN and BELL, *Proc. Roy. Soc.* (London), **A158**, 464 (1937).

The ratio of the relative amounts of ortho and para substituted products is therefore independent of time, and the ratio of the specific rates k_o/k_p may be determined by determining the relative amounts of the two products, either after reaction is complete or earlier if desirable. If, further, one determines the way in which the composition of the reaction product varies with temperature, one may calculate the quantities

$$\Delta H_o{}^{\ddagger} - \Delta H_p{}^{\ddagger} = \frac{RT^2\, \mathrm{d}[\ln\,(k_o/k_P)]}{\mathrm{d}T} \tag{82}$$

$$\Delta S_o{}^{\ddagger} - \Delta S_p{}^{\ddagger} = \frac{\mathrm{d}[RT\,\ln\,(k_o/k_P)]}{\mathrm{d}T} \tag{83}$$

The entropy differences thus obtained have been found[29] to be small (Table II) in all the cases investigated and are probably within the experimental error, because they are largest in those cases in which the proportion of one product is so small that the error in its measurement is large. Consequently, the orientation of substituents in the benzene ring is another case in which the potential-energy quantity ΔE_P may be approached from rate measurements—another case in which the structural problem is an especially simple one. In this case, moreover, the relative rate of reaction in the ortho position is just as much a purely potential-energy problem, free of kinetic-energy complications, as it is in the other positions.

The constancy of the entropy of activation has an important practical effect. By equation (83) it implies a zero value of the derivative in that equation, from which

$$RT\,\ln\frac{k_o}{k_p} = \text{a constant} \tag{84}$$

In order that this equation be satisfied, it is necessary that $\ln\,(k_o/k_p)$ approach zero and k_o/k_p approach unity as T increases toward infinity. If the ratio of the rates is greater than one, it must therefore decrease, if less than one, it must increase as the temperature rises. Except for minor complications due to statistical factors, such as the 2 in equation (79), the proportion

[29] Scheffer and Brandsma, *Rec. trav. chim.*, **45**, 522 (1926). Bradfield and Jones, *J. Chem. Soc.*, 1006 (1928).

of the substance formed in smaller amount must also increase with rising temperature.

Even when there are differences in the entropies of activation, a similar although approximate conclusion may frequently be drawn. This furnishes an explanation for the generalization, familiar to practicing organic chemists, that a low temperature tends to reduce the proportion of minor by-products and, consequently, to improve the yield and ease of purification of a major product.

TABLE II.—RELATIVE RATES AND ENTROPY OF ACTIVATION DIFFERENCES IN ORIENTATION IN THE BENZENE RING[29]

Reaction	Positions involved	Relative rates, 0°c	Entropy dif.
Nitration of chlorbenzene................	o/p	0.215	−0.5
Nitration of brombenzene...............	o/p	0.303	0.0
Nitration of iodobenzene................	o/p	......	−0.5
Nitration of benzoic acid................	o/m	0.230	+2.0
Nitration of ethyl benzoate.............	o/m	0.414	−1.4
Nitration of toluene.....................	o/m	14.9	+3.1
Nitration of toluene.....................	o/p	0.761	+0.5
Bromination of toluene..................	o/p	......	+1.0
Nitration of 3-chlorbenzoic acid	⅔	0.087	−2.3
Nitration of 3-brombenzoic acid..........	⅔	0.15	−0.2
Nitration of 1,3-dichlorbenzene..........	⅔	0.040	0.0
Nitration of 1,2-dichlorbenzene	¾	0.078	+0.9
Nitration of 2-chlorbenzoic acid..........	⅗	0.19	−0.5
Nitration of 2-brombenzoic acid..........	⅗	0.245	0.0

Entropy of Activation and Molecular Complexity.—The entropy of activation for the reaction in the gas phase of cyclopentadiene with α-naphthoquinone is 5.3 cal./deg. less than for the reaction with benzoquinone; that for the reaction of a second molecule of cyclopentadiene with cyclopentadiene benzoquinone is 2.2 units less than for the reaction of the first molecule with benzoquinone.[30] If the decrease in entropy of activation with molecular complexity thus indicated is general, it will go far to account for the well-known fact that polymerization reactions

[30] WASSERMANN, *Trans. Faraday Soc.*, **32**, 69 (1936).

slow down as the degree of polymerization increases.[31]   The decrease in entropy with increasing molecular size implies a decrease in the kinetic-energy terms of the fundamental rate equation.   Since the potential-energy term can be affected only slightly, the rate must decrease.

The Brønsted Rate Equation.—The transition-state theory is consistent with the important rate equation of Brønsted[32] which describes the effect of the medium upon reaction rate.   If the rate expressions

$$\left.\begin{array}{l} v_1 = k_1[A][B] \\ v_{-1} = k_{-1}[C][D] \end{array}\right\} \tag{85}$$

for the forward and reverse reactions

$$A + B \rightleftharpoons C + D \tag{XI}$$

are to be made consistent with the exact equilibrium expression

$$\frac{[C][D]}{[A][B]} = K\frac{f_A f_B}{f_C f_D} \tag{86}$$

they must be altered at least by the inclusion of the activity coefficients of reactants and products as factors.   The simplest hypothesis, *viz.*, that

$$\left.\begin{array}{l} v_1 = k_1[A][B]f_A f_B = k_1 a_A a_B \\ v_{-1} = k_{-1}[C][D]f_C f_D = k_{-1} a_C a_D \end{array}\right\} \tag{87}$$

is unsatisfactory because it leads to the entirely incorrect conclusion that the rates of all reactions between ions must be decreased by increase in ionic strength.

Most chemists were prevented from even approaching this problem by one of those generalizations from insufficient data which have so often plagued physical chemistry, *viz.*, the conclusion that all reactions between ions are too fast to be measured. Brønsted, being well-schooled in the chemistry of the cobaltammines, knew that this is not so and was led by observation of the behavior of such reactions to the equations

[31] BAWN, *Trans. Faraday Soc.*, **32**, 178 (1936). DOSTAL and MARK, *Angew. Chem.*, **50**, 348 (1937). DOSTAL, *Monatsh.*, **67**, 63 (1936). FLORY, *J. Am. Chem. Soc.* **61**, 3334 (1939).

[32] BRØNSTED, *Z. physik. Chem.*, **102**, 169 (1922).

$$v_1 = k_1[A][B]\frac{f_A f_B}{f_x}\ .$$

$$v_{-1} = k_{-1}[C][D]\frac{f_C f_D}{f_x} \tag{88}$$

Here f_x is the activity coefficient of the "critical complex," a half-reacted state, identical for forward and reverse reactions, which is obviously equivalent to the transition state of the theory of that name.   The equations are consistent with the equilibrium law, because f_x cancels out when v_1 is set equal to v_{-1}.

The value of f_x is not directly measurable but is predictable for reactions between ions in dilute solution, because the charge on the critical complex is necessarily the algebraic sum of the charges on the reacting ions.   When A and B are singly charged ions of opposite sign, f_x is the coefficient of a neutral molecule and is relatively unaffected by changes in ionic strength or nature of the medium.   Since f_A and f_B decrease with increasing ionic strength, the addition of salt must decrease the rate of reaction. If, however, A and B have the same sign, f_x is the coefficient of a doubly charged ion, which decreases more rapidly with increasing ionic strength than does the product $f_A f_B$.   Consequently, the addition of salt increases the rate of reaction.   If, finally, A is an ion and B an uncharged molecule, the critical complex will be an ion of the same charge as A.   Neither the ratio f_A/f_x nor f_B is much affected by changes in ionic strength, and the addition of salt has little effect upon the rate.   The negative, the positive, and the null salt effects thus predicted have been observed in a wide variety of reactions.   The verification of equation (88) becomes quantitative when the ionic strength is so low that the Debye-Hückel expression for the variation of activity coefficient with ionic strength is applicable.[32,33]

Unfortunately, the activity coefficient of the transition state is predictable only in the limited case of very dilute solutions of electrolytes in a solvent of reasonably high dielectric constant and is not in any case accessible to independent direct measurement.   This limits the application of the Brønsted equation, although there can be no doubt of its general validity.

The transition-state theory supposes that the rate of any reaction is given by the product of the concentration of molecular

[33] LaMer, *Chem. Rev.*, **10**, 179 (1932).

groupings in the transition state by a constant rate [equation (66)]. The application of exact rather than approximate thermodynamics gives for the concentration $c^{\ddagger}$ of systems in the transition state of reaction (XI)[16]

$$\frac{c^{\ddagger}}{[A][B]} = K^{\ddagger}\frac{f_A f_B}{f^{\ddagger}}$$ (89)

Consequently, the rate v is given by

$$v = \tfrac{1}{2}v^{\ddagger}K^{\ddagger}[A][B]\frac{f_A f_B}{f^{\ddagger}}$$ (90)

and the specific rate k by

$$k = \tfrac{1}{2}v^{\ddagger}K^{\ddagger}\frac{f_A f_B}{f^{\ddagger}}$$ (91)

which is equivalent to the Brønsted equation.

The Importance of a Constant Medium in Kinetic Investigations.—Because of the presence of the activity coefficients in the exact rate equation [(88)], valid conclusions with respect to reaction order and mechanism can be drawn only from experiments in which the nature of the medium is nearly constant. With respect to reactions in solution this requires that the effect of varying concentration of the reactants be observed in solutions in a single solvent or mixture of solvents of constant composition and that the only variable concentrations be those of solutes present in relatively dilute solution. The failure to recognize this fundamental limitation has been a fertile source of error in the interpretation of kinetic data on reaction mechanisms.

When the reactions involve ʻions, the limitation is especially important because the rate is so sensitive to ionic strength. The stratagem of using a high and relatively constant ionic strength is just as effective in the rate problem as in the equilibrium one (page 94) and has played an important role in recent investigations of the catalytic effect of acids and bases (page 216).

Reactions in the Gas Phase and in Solution.—It is only in the gas phase that the frequency of collisions between reacting molecules can be calculated with any certainty. In the light of the collision theory the study of reaction kinetics should, therefore, begin with and constantly refer back to reactions in

the gas phase.   In terms of the transition-state theory, however, this supposed advantage of the gaseous state loses much of its weight because the collision frequency does not enter into the theory and the parallelism between dilute gas and dilute solution is just as useful [equation (91)] as it is for purely thermodynamic problems.

In any case, very few of the reactions of organic chemistry that are carried out in the liquid phase can be referred to the gaseous state as a standard because they either completely and obviously refuse to take place in the gaseous state or appear to take place only because the reaction occurs on the walls of the container.   This has been proved with the following familiar reactions: the acid-catalyzed depolymerization of paraldehyde,[34] the hydrolysis of benzyl chloride,[35] the conversion of methanol to methyl chloride or to methyl acetate,[36] the hydrolysis of ethyl acetate,[36] the reaction of triethylamine with ethyl iodide,[37] and that of acetic anhydride and ethanol.[37]

These reactions are of a very common type which is either initiated by ions or forms ions as intermediates or final products (page 151); the energy required to form an ion in the gas state is prohibitively large.   The reactions occur, therefore, only in polar solvents in which the energy of an ion is smaller.   By contrast, the typical reaction in the gas phase is initiated by or involves the transient formation of atoms or radicals (page 379). Reactions of the radical type do occur in solution, but the ionic type apparently offers in most cases a path of lower energy.

[34] BELL and BARNETT, *Trans. Faraday Soc.*, **33**, 355 (1937).

[35] HARKER, *J. Chem. Soc.*, **125**, 500 (1924).

[36] WINKLER and HINSHELWOOD, *Trans. Faraday Soc.*, **31**, 1739 (1935).

[37] MOELWYN-HUGHES and HINSHELWOOD, *J. Chem. Soc.*, 230 (1932).

CHAPTER V

THE DISPLACEMENT REACTION

The Mechanism of the Displacement Reaction.—By far the most important type of reaction in organic chemistry and probably in all chemistry is the displacement the general symbol of which is

$$A + BC \rightarrow AB + C \tag{I}$$

A, B, and C may be atoms or groups of atoms, charged or uncharged. An obvious example is the second-order reaction of an alkyl halide with hydroxyl ion, *e.g.*,

$$CH_3I + OH^- \rightarrow CH_3OH + I^- \tag{II}$$
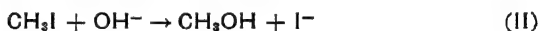
in which hydroxyl ion displaces iodide ion from its combination with carbon. The process is also involved in a great many reactions which are not obviously displacements ·but which kinetic investigation has shown to consist of a series of reactions of that type. The prevalence of this kind of reaction can mean only that it encounters less resistance than alternative reaction paths; even making all necessary allowance for the effect of the kinetic-energy terms in the rate equation, it means that the energy barriers to be surmounted are lower for displacements as a group than for other types of reaction.

The low barrier can be understood in terms of a picture of the reaction process the application of which to organic chemistry is due to Polanyi,[1] although the fundamental method was first used by London[2] for the reactions of simpler substances. The problem is basically one of the energy of a system of three atoms or groups of atoms, which are capable of forming the two stable compounds AB and BC. The energy ϕ of a BC molecule in the absence of the A atom depends upon the distance r_{BC} in the way shown in curve a of Fig. 1 (see page 31). Because of the char-

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[1] Reviewed by Evans and Polanyi, *Trans. Faraday Soc.*, **34**, 11 (1938).

[2] LONDON, *Z. Elektrochem.*, **35**, 552 (1929).

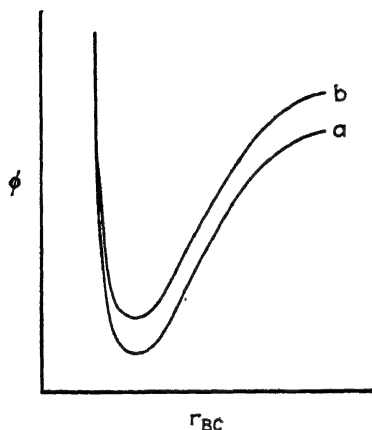acteristic repulsion that stable molecules exert on other molecules or atoms at close distances (page 12), it will require the expenditure of work to bring an A atom into the neighborhood of the BC molecule. Consequently, the energy of the system will be higher when A and BC are close together, and a plot of energy against r_{BC} will be higher, as in curve *b* of Fig. 1. With closer approach the energy increases further and must be represented by still higher curves.

A complete treatment would consider the angle ABC as well as the distances but is fortunately unnecessary for the reaction-rate problem. Because of the exponential dependence of rate upon energy, the rate problem reduces to the determination of the lowest energy barrier that may be surmounted, any other reaction path being of subordinate importance. Now A is

Fig. V-1.—The energy of a BC molecule in the absence (*a*) and the presence (*b*) of an A atom.
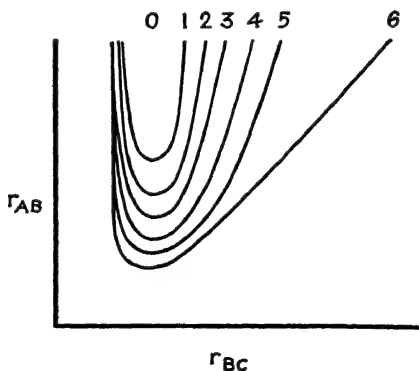

Fig. V-2.—Energy contours for a BC molecule in the presence of an A atom.

repelled by both B and C, especially, however, by the latter with which it cannot form a stable compound. The easiest way, the one requiring the smallest expenditure of energy, by which A

may approach B is, therefore, the one that keeps A as far as possible from C; this configuration, in which the three atoms lie in a straight line, is the only one that need be considered.

Potential-energy Diagrams.—Figure 1 attempts to represent in two dimensions the three-dimensional relationship by virtue of which the energy ϕ is a function of two distances r_{BC} and the distance between A and B, r_{AB}. An alternative and instructive representation is a contour map of the energy in terms of the two distances, such as Fig. 2. The lines join points for which ϕ has a constant value.
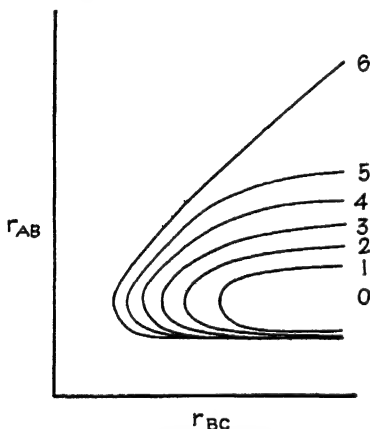

Fig. V-3.—Energy contours for an AB molecule in the presence of a C atom.
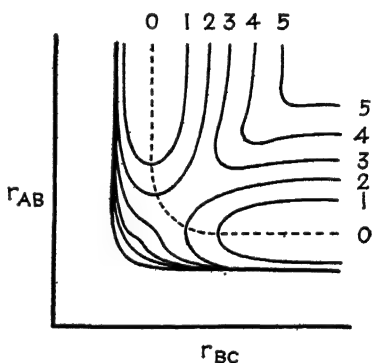
Fig. V-4.—Energy contours for a system of A, B, and C atoms.

The same kind of analysis of the reverse reaction, which considers the effect of a C atom upon the dissociation energy of the AB molecule, leads to a similar plot, but one that is rotated 90 deg., as in Fig. 3. A system composed of an A atom and a BC molecule is not, however, really different from one composed of a C atom and an AB molecule; these are merely two possible ways of looking at the system of three atoms, and the two diagrams are two possible approximations. The actual energy will in no case be higher than that given by either approximation; because of resonance it tends to be lower than either. The two diagrams must, therefore, be combined by taking for each point the lower of the two values given by Fig. 2 or 3 and

rounding off the resulting sharp angles in a way that corresponds to the existence of the resonance. The result is shown in Fig. 4 and represents two valleys at right angles, joined by a pass the altitude of which is considerably lower than the flat tableland which corresponds to complete dissociation into the three atoms A, B, and C.

A point at the bottom of the valley at the top left represents a BC molecule with an A atom at a large distance from it; one at the bottom of the valley to the lower right represents an AB molecule with a C atom at a large distance. Consequently, the transfer of a representative point from the first to the second position symbolizes the reaction of equation (I). The path by which this may occur with the smallest expenditure of energy is that represented by the dotted line of Fig. 4, in which the representative point travels up the bottom of one valley, crosses the pass at a relatively low altitude, and then follows down the floor of the other valley. This must be overwhelmingly the most probable course for the reaction.

Chemical Inertia and Chemical Driving Force.—It is a most important feature of this picture that the energy required for the reaction is considerably less than that required to dissociate the BC molecule into B and C. The latter process is represented by the motion toward the upper right of the diagram of the point representing the state of the system, and this obviously requires much more energy than the traversal of the pass. This striking result is indeed a direct corollary of the nature of the system when it has just reached the top of the pass. At this point it is no longer a BC molecule with a separate A atom nor has it yet become an AB molecule with a separate C atom, it is something in between and in the course of changing from the one to the other. The AB molecule begins, therefore, to form before the BC molecule has completely dissociated, and the energy of formation of the new molecule is to a certain extent utilized in disrupting the old one. Evans and Polanyi[1] have introduced the important and useful terms *chemical driving force* and *chemical inertia* in connection with this situation. By chemical inertia is meant the work that must be done to produce reaction, partly in breaking existing bonds, partly in overcoming the repulsions of the reacting molecules. By chemical driving force is meant the

contribution that the energy of formation of new bonds makes toward the overcoming of this inertia. The difference is the necessary potential energy of activation.

The system, when its representative point is at the top of the pass, is clearly in the transition state of the last chapter. Its nature as something intermediate between AB and BC molecules is also borne out by the interatomic distances: the distance r_{BC} is greater than it was in the stable BC molecule, the distance r_{AB} is not so small as it will become in the stable AB molecule. The energy required to bring the representative point from the original valley bottom to the top of the pass is the $\Delta E_P^{\ddagger}$ of the last chapter; actual energies and free energies of activation differ from it by virtue of the presence of kinetic energy in both reactants and transition state.

Quantitative Approaches: Double Decompositions.—The London treatment has been developed quantitatively for application to reactions involving a free and unsaturated atom.[3] Such are, for instance, the reactions

$$H + Cl_2 \rightarrow HCl + Cl \qquad (III)$$
$$Cl + H_2 \rightarrow HCl + H \qquad (IV)$$

which are known as important steps in the chain mechanism by which the reaction of hydrogen and chlorine takes place (page 368), and the isotopic exchanges

$$D + H_2 \rightarrow DH + H \qquad (V)$$

A similar treatment may be applied to true double decompositions,[3] such as

$$H_2 + I_2 \rightarrow 2HI \qquad (VI)$$

In this it appears that the molecules must approach side by side, the larger iodine molecule stretching out until it finally engulfs the hydrogen molecule. The atoms of the latter also separate, but less rapidly, combining simultaneously with the iodine atoms. In the transition state, both iodine and hydrogen molecules are partly disrupted and hydrogen iodide molecules are partly formed. Double-decomposition reactions appear to be less

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[3] EYRING, *J. Am. Chem. Soc.*, **53**, 2537 (1931); *Trans. Faraday Soc.*, **34**, 3 (1938).

common than the displacement types, but their possibility must not be overlooked in discussions of mechanism.

Semiquantitative attacks have also been made[1] on the question of displacements involving valence-saturated structures, such as that of equation (II), but the problem is a more difficult one.

Relations between Binding Energies, Rates, and Equilibria.—Probably the most important result of the Polanyi picture of the displacement reaction is the prediction that it permits of a relationship between the height of the pass $\Delta E_P{}^{\ddagger}$ and the strength of the linkages in the molecules BC and AB.[1,4] Given the reactions (I) and (VII)

$$A + BC' \rightarrow AB + C' \tag{VII}$$

which differ only in the substitution of the atom or group C′ for C, the formation of the transition state requires the expenditure of a certain amount of work against the binding forces of the molecules BC or BC′. If the binding energy is greater in the first molecule, there is every reason to expect that the energy required to attain the transition state will be greater also. The greater energy of binding in the reacting molecule is likely, therefore, to be accompanied by a greater potential energy of activation. Less directly and less certainly, because of the kinetic-energy terms in the equilibrium and rate equations, it is likely to be accompanied by greater free energy of reaction and of activation, hence by decreased equilibrium and rate constants. The Polyani picture predicts, therefore, that a variation in the group C in the type reaction (I) should produce a general and approximate parallelism between the equilibrium constants and the rate constants of the resulting series of reactions and that the smaller values of both constants should appear in those cases in which the strength of the BC linkage is greatest.

When the group A is varied, an increase in the strength of the AB binding must decrease the work required to attain the transition state because this linkage furnishes the driving force of the reaction. Consequently, a general parallelism between rate and equilibrium constants is to be expected in this case also,

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[4] HAMMETT and PFLUGER, *J. Am. Chem. Soc.*, **55**, 4079 (1933). HAMMETT, *Chem. Rev.*, **17**, 125 (1935). OGG and POLANYI, *Trans. Faraday Soc.*, **31**, 604 (1935).

with smaller values of both corresponding to weaker values of binding energy in the AB molecule.

When the group B is varied, the parallelism between rate and equilibrium cannot be expected to apply, because the energies of binding of both BC and AB are varied. If, as is possible, both energies increase by the same amount, the total energy change of the reaction will not be altered, but the energy required to attain the transition state will increase. A large decrease in rate will then be accompanied by a relatively small change in equilibrium constant. An extreme case appears in racemizations, in all of which the equilibrium constant, the ratio of dextro- to levo-form at equilibrium, has the value of unity. The rates, on the other hand, vary from the unobservably small to the unobservably great. Even in this case, however, strong linkages are likely to result in low reaction rate; the parallelism between energy of binding and rate should persist although that between rate and equilibrium disappears.

The existence of parallelisms of this kind has been a widely accepted, although not always explicitly stated, principle of the practicing organic chemist. Aside from any theory it possesses, the ultimate justification is that it is satisfied in a sufficient variety of cases to make it a useful working rule; it may even be given quantitative expression for restricted groups of related reactions (page 215). It must, however, be used with care for its limitations, the guiding rule being that its precision and reliability are greater, the more closely related are the reactions to which it is applied.

Because the principle has lacked until recently any theoretical background, because there are striking exceptions, and because it has sometimes been confused with the quite different effect of the displacement of the equilibrium of a reaction toward greater completeness by suppression of the reverse reaction, the physical chemist has tended to be scornful of the possibility of parallelisms between rate and equilibrium. The impossibility of their existence has even at times been erected into dogma, using as an example the racemization or the notable sluggishness of the reaction of hydrogen and oxygen. The racemization, however, fits satisfactorily into the frame of the Polanyi picture. The hydrogen-oxygen case disproves any general parallelism between

the rates and the equilibria of all reactions; it has no application to the question of a restricted parallelism in systems of related reactions.

Aside from qualitative or even quantitative parallelisms of this sort, the great merit of the Polanyi analysis is that it answers one of the most puzzling questions of organic chemistry: Why is it that a compound that resists change over long periods of time, even though the system may be thermodynamically unstable, reacts readily in the presence of specific reagents? In the light of this analysis it is rapidly becoming apparent that the reagents which are effective in this sense are those which can enter into displacement reactions in such a way that the energy of formation of a new linkage contributes toward the rupture of an old—that the search for synthetic methods has been to a large extent a search for usable chemical driving forces.

The Reaction of Alkyl Halides with Mercuric and Silver Salts. In the sense of the last paragraph, silver and mercuric salts are specific reagents for alkyl halides. This property of silver salts is a familiar fact of preparative chemistry, from which it is well known that silver oxide greatly accelerates the hydrolysis of the halide, and that halides react very much more rapidly with silver acetate than with sodium acetate in the synthesis of alkyl acetates. Although the fact is less familiar, mercuric salts are quite as effective as those of silver. It can hardly be a coincidence that the two substances silver ion and mercuric ion which are most notable for their affinity for halide ion should be the ones which most effectively activate reactions involving the separation of halide ion from an alkyl group. The evidence for the affinity is the small ionization of the mercuric halides, the insolubility of the silver halides, and the fact that silver halides dissolve in excess of halide ion to form complexes of the nature of $AgI_2.^-$ It is, therefore, probable that other ions that form moderately stable complex halide ions, such as copper, cadmium, and lead, will also accelerate the reactions of alkyl halides.
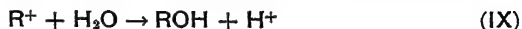
If the driving force of these reactions comes from the attack of the metallic ion on the halogen, there are two possible modes of action between which a distinction is possible by kinetic methods.[5] Either the metallic ion simply removes the halide ion, leaving the

[5] Roberts and Hammett, *J. Am. Chem. Soc.*, **59**, 1063 (1937).
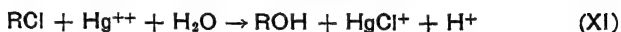
alkyl residue as a carbonium ion

$$RCl + Hg^{++} \rightarrow R^+ + HgCl^+ \tag{VIII}$$

which later reacts with a solvent molecule or a negative ion

$$R^+ + H_2O \rightarrow ROH + H^+ \tag{IX}$$

or

$$R^+ + NO_3^- \rightarrow RNO_3 \tag{X}$$

Or the process is a single termolecular one, thus

$$RCl + Hg^{++} + H_2O \rightarrow ROH + HgCl^+ + H^+ \tag{XI}$$

or

$$RCl + Hg^{++} + NO_3^- \rightarrow RNO_3 + HgCl^+ \tag{XII}$$

In the case of the reaction with silver ion there are complications arising from the fact that the reaction is catalyzed by solid silver halide and is, therefore, largely heterogeneous. There are also some difficulties of interpretation in the homogeneous reaction with mercuric ion, which apparently result from the great tendency of mercuric ion to form complex compounds. A solution of mercuric nitrate contains such substances as $Hg(H_2O)_4^{++}$, $Hg(H_2O)_3(NO_3)^+$, $Hg(H_2O)_2(NO_3)_2$, and perhaps others, along with little if any uncombined mercuric ion. By analogy, a solution of the perchlorate contains $Hg(H_2O)_3(ClO_4)^+$, etc. Each of these substances appears to have its own specific rate of reaction with alkyl halide, with the nitrate complexes, and to a greater extent the perchlorate complexes, more reactive than the hydrate. The situation is similar to the general acid catalysis (page 215) in which all compounds of hydrogen react with a substrate, each at its own specific rate. Consequently, sodium nitrate and other nitrates increase the rate of reaction of mercuric nitrate with benzyl chloride, and sodium perchlorate produces a still greater acceleration. It is, therefore, impossible to decide between the mechanism of reactions (VIII), (IX), and (X) and that of reactions (XI) and (XII) in terms of the acceleration produced by nitrate ion. The distinction is, however, possible upon the basis that the termolecular mechanism requires a simple relationship between the effect of nitrate ion upon the total rate of reaction of benzyl chloride and upon the relative amounts of benzyl alcohol and benzyl nitrate formed. The complete failure of this relationship to appear indicates strongly that the mechanism is the carbonium ion one of equations (VIII) to (X). In

this the total rate of reaction is that of equation (VIII), whereas the composition of the product is determined by the relative rates of reactions (IX) and (X). In view of the probability that the ion $C_6H_5CH_2^+$ is colored, the yellow color that appears during the course of the mercuric nitrate-benzyl chloride reaction and disappears as the reaction approaches completion is a confirmation of the mechanism.

Acceleration of Forward or Suppression of Reverse Reaction.— The acceleration of the hydrolysis of an alkyl halide by mercuric ion is an entirely different phenomenon from the suppression of the reverse reaction, which is so familiar in the chemistry of electrolytes. There are, in principle, two possible reasons why the reaction

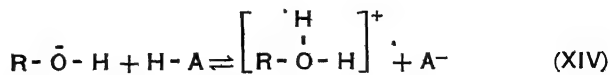$$C_6H_5CH_2Cl + H_2O \rightarrow C_6H_5CH_2OH + H^+ + Cl^- \qquad (XIII)$$
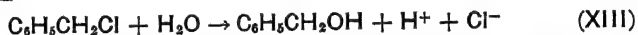
might fail to go at an observable rate. The reaction might be inherently slow, or it might be a fast one accompanied by an even more rapid reverse process. The latter hypothesis requires that mercuric or silver ion should suppress the reverse reaction by combining with the chloride ion, thus permitting the hydrolysis to proceed; it also requires that the reaction of benzyl alcohol with hydrochloric acid should be rapid, which is not in fact the case.

**Other Electrophilic Displacements: Condensation Reactions.—** The driving force of the benzyl chloride-mercuric ion reaction is the tendency of mercuric ion to attain a filled shell of valence electrons by sharing the electrons of the chlorine, which carries three unshared pairs. Mercuric ion may, therefore, be called an *electrophilic* or electron-seeking reagent[6] and the reaction of equation (VIII) an *electrophilic displacement on chlorine*.

A similar process is possible whenever a compound containing unshared electrons is treated with a reagent with a large affinity for electrons. Thus an alcohol, or any other oxygen compound, carries unshared electrons on the oxygen; a strong acid contains loosely bound protons. Hence, there must be considerable tendency for the reaction

$$R \text{-} \overset{\cdot\cdot}{\underset{\cdot\cdot}{O}} \text{-} H + H \text{-} A \rightleftharpoons \left[R \text{-} \overset{\overset{\cdot}{H}}{\underset{\cdot\cdot}{\underset{|}{O}}} \text{-} H \right]^+ + A^- \qquad (XIV)$$
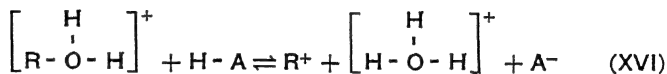
[6] Hughes and Ingold, *J. Chem. Soc.*, **244**, (1935).

The addition of the proton must displace the electron system in such a way as to weaken the R—O bond and favor the rupture

$$\left[\begin{array}{c} H \\ | \\ R\text{-}O\text{-}H \end{array}\right]^{+} \rightarrow R^{+} + H\text{-}\ddot{O}\text{-}H \qquad \cdot \quad (XV)$$
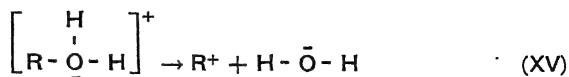
which must be still further favored by the reaction of a second mole of acid

$$\left[\begin{array}{c} H \\ | \\ R\text{-}O\text{-}H \end{array}\right]^{+} + H\text{-}A \rightleftharpoons R^{+} + \left[\begin{array}{c} H \\ | \\ H\text{-}O\text{-}H \end{array}\right]^{+} + A^{-} \qquad (XVI)$$

The over-all effect of reactions (XIV) and (XV) or (XIV) and (XVI) is the displacement of the R^{+} ion from combination with oxygen by a proton, the driving force being the affinity of the proton for the oxygen electrons. The reaction is, therefore, an electrophilic displacement on oxygen. A carbonium ion is a most reactive entity, and its formation and subsequent reaction represent a satisfactory mechanism for the wide variety of reactions into which alcohols may enter in the presence of strong acids (page 296). A notable example is the nuclear alkylation of aromatic hydrocarbons that occurs in the presence of 70 to 80 per cent aqueous sulfuric acid.[7]

The same reactions may be produced by the action of boron trifluoride instead of sulfuric acid.[8] Boron fluoride is one of the most powerfully electrophilic substances known, because the boron carries only six valence electrons, whereas its filled shell contains eight. It reacts readily with fluorine compounds to form the stable ion BF_4^{-}, with hydroxyl compounds to form BF_3OH^{-}, and with ammonia to form BF_3NH_3; the source of energy being in every case the tendency of the boron to complete the octet
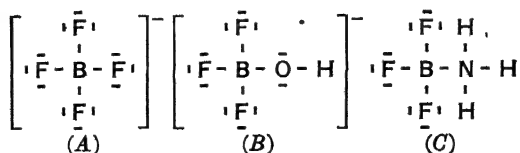
[7] MEYER and BERNHAUER, *Monatsh.*, **53/54**, 721 (1929).

[8] (*a*) MEERWEIN, *Ber.*, **66B**, 411 (1933). (*b*) CROXALL, SOWA, and NIEULAND, *J. Org. Chem.*, **2**, 253 (1937).

Once attached to oxygen the boron lays claim to the available electrons so strongly as to weaken all the other linkages of the oxygen. Thus the hydrate (D) is an extremely strong acid[8a]

$$
\begin{array}{cc}
\quad \ \ {}_{\textrm{\tiny I}}\bar{\textrm{F}}{}_{\textrm{\tiny I}}\ \ \textrm{H} & \quad \ \ {}_{\textrm{\tiny I}}\bar{\textrm{F}}{}_{\textrm{\tiny I}}\ \ \textrm{H} \\[-4pt]
\quad \ \ \ \ | \ \ \ \ | & \quad \ \ \ \ | \ \ \ \ | \\[-4pt]
{}_{\textrm{\tiny I}}\bar{\textrm{F}} - \textrm{B} - \underset{\cdot\cdot}{\textrm{O}} - \textrm{H} & {}_{\textrm{\tiny I}}\bar{\textrm{F}} - \textrm{B} - \underset{\cdot\cdot}{\textrm{O}} - \textrm{CH}_3 \\[-4pt]
\quad \ \ \ \ | & \quad \ \ \ \ | \\[-4pt]
\quad \ \ {}_{\textrm{\tiny I}}\bar{\textrm{F}}{}_{\textrm{\tiny I}} & \quad \ \ {}_{\textrm{\tiny I}}\bar{\textrm{F}}{}_{\textrm{\tiny I}} \\[2pt]
\quad (D) & \quad (E)
\end{array}
$$
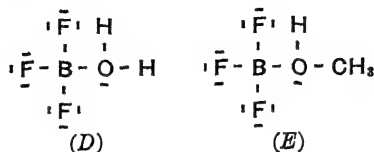
so strong that it forms a stable crystalline oxonium salt (page 43). The alcohol analogues, such as (E), are not only strong acids, but also very active alkylating agents by virtue of the weakening of the C—O link. Even more effective for the latter purpose is the combination of boron fluoride and methyl fluoride (page 44).

For the same reason $AlCl_3$ is also a powerful electrophilic reagent, and the driving force of the Friedel-Crafts reaction is its tendency to make up an octet of shared electrons by attacking the unshared pairs of chlorine atoms. Since indeed the formation of complexes of the type of BF_4^- and $AlCl_4^-$ is a very general property of metallic ions, the ability to act as an electrophilic reagent is of common occurrence in the compounds of all the metals except the alkalies and alkaline earths. A typical example is zinc chloride, which is frequently useful as a condensing agent.[9] The importance of such electrophilic reagents as the equivalent of strong acids (proton donors) has recently been emphasized by G. N. Lewis.[10]
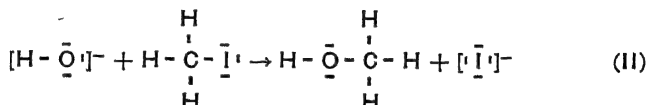
Whether a carbonium ion is set free as an intermediate in condensation reactions is a problem for investigation in each case, since the alkyl group may be transferred to a new linkage without actually being liberated. In any case the driving force is the affinity of the electrophilic reagent for the halogen or oxygen electrons. These reactions are, therefore, excellent examples of the use of a reagent with an affinity for the reaction product to speed up a reaction.

Nucleophilic Displacements on Carbon and on Hydrogen.— Another important reaction type involves the direct displacement
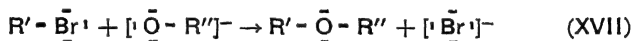
[9] MEERWEIN, *Ann.*, **455**, 227 (1927).
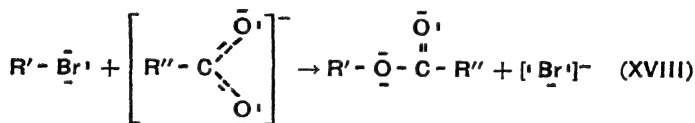[10] *J. Franklin Inst.*, **226**, 293 (1938).

of one group attached to carbon by another that carries an unshared electron pair. It may be called a *nucleophilic displacement on carbon;* nucleophilic because the driving force is the nucleus-seeking tendency of the unshared pair, on carbon because it involves the displacement of one group attached to carbon by another. A familiar example is reaction (II), which may be written in more detail as

$$[H - \bar{O} \cdot]^- + H - \underset{\underset{H}{|}}{\overset{\overset{H}{|}}{C}} - \bar{I} \cdot \rightarrow H - \bar{O} - \underset{\underset{H}{|}}{\overset{\overset{H}{|}}{C}} - H + [\cdot \bar{I} \cdot]^- \qquad (II)$$
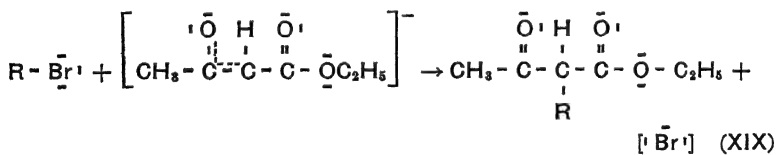
The second-order kinetics and the stereochemical effects (page 160) leave no doubt that reactions of this type do follow the course of simultaneous formation of new and rupture of old bonds and that the driving force is the affinity of the oxygen electrons for carbon. A similar process is involved in the Williamson ether synthesis

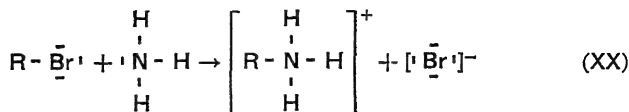$$R' - \bar{B}r \cdot + [\cdot \bar{O} - R'']^- \rightarrow R' - \bar{O} - R'' + [\cdot \bar{B}r \cdot]^- \qquad (XVII)$$

in the reaction

$$R' - \bar{B}r \cdot + \left[R'' - C \underset{\overset{}{\underset{O \cdot}{}}}{\overset{\overset{\bar{O} \cdot}{\diagup}}{\diagdown}} \right]^- \rightarrow R' - \bar{O} - \overset{\overset{\bar{O} \cdot}{\|}}{C} - R'' + [\cdot Br \cdot]^- \qquad (XVIII)$$

and in the alkylation of sodium acetacetic ester

$$R - \bar{B}r \cdot + \left[CH_3 - \overset{\overset{\cdot \bar{O}}{\|}}{C} \text{---} \overset{\overset{H}{|}}{C} - \overset{\overset{\bar{O} \cdot}{\|}}{C} - \bar{O}C_2H_5 \right]^- \rightarrow CH_3 - \overset{\overset{\bar{O} \cdot}{\|}}{C} - \underset{\underset{R}{|}}{\overset{\overset{H}{|}}{C}} - \overset{\overset{\bar{O} \cdot}{\|}}{C} - \bar{O} - C_2H_5 +$$

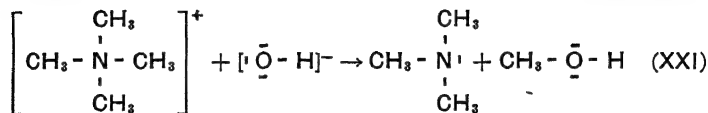$$[\cdot \bar{B}r \cdot] \qquad (XIX)$$

In spite of seeming differences due to a variation in electrical charge type, the same process[11] is involved in the alkylation of amines

[11] (*a*) HANHART and INGOLD, *J. Chem. Soc.*, 997 (1927). (*b*) HUGHES, INGOLD, and PATEL, *ibid.*, 526 (1933). (*c*) GLEAVE, HUGHES, and INGOLD, *ibid.*, 236 (1935).
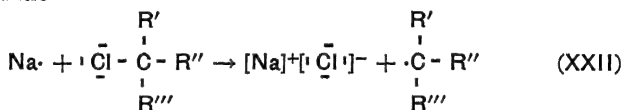
$$R - \bar{B}r \cdot + \cdot \overset{\overset{\displaystyle H}{|}}{\underset{\underset{\displaystyle H}{|}}{N}} - H \rightarrow \left[R - \overset{\overset{\displaystyle H}{|}}{\underset{\underset{\displaystyle H}{|}}{N}} - H \right]^+ + [\cdot \bar{B}r \cdot]^- \qquad (XX)$$

and in the decomposition of quaternary ammonium hydroxides

$$\left[\overset{\overset{\displaystyle CH_3}{|}}{CH_3 - \underset{\underset{\displaystyle CH_3}{|}}{N} - CH_3} \right]^+ + [\cdot \bar{O} - H]^- \rightarrow CH_3 - \overset{\overset{\displaystyle CH_3}{|}}{\underset{\underset{\displaystyle CH_3}{|}}{N}} \cdot + CH_3 - \bar{O} - H \qquad (XXI)$$

All proton-transfer reactions (page 49) are by the same token *nucleophilic displacements on hydrogen.*

Atom or Radical Displacements on Halogen.—When the displacing group is an atom or radical and reacts by virtue of a single unshared electron, the process may be called a *radical displacement.* The most fully investigated example of this process is the reaction in the gas phase between atomic sodium and alkyl halide

$$Na\cdot + \cdot \bar{C}l - \overset{\overset{\displaystyle R'}{|}}{\underset{\underset{\displaystyle R'''}{|}}{C}} - R'' \rightarrow [Na]^+[\cdot \bar{C}l \cdot]^- + \cdot \overset{\overset{\displaystyle R'}{|}}{\underset{\underset{\displaystyle R'''}{|}}{C}} - R'' \qquad (XXII)$$

The reaction is much too rapid for ordinary methods of measurement, and an ingenious scheme was developed[12] which depends upon bringing together gaseous currents of the reactants at low pressures and determining by optical methods the dimensions of the zone that carries unreacted sodium vapor. The larger the zone, the slower the reaction. The demonstration of the presence of methyl, ethyl, and phenyl radicals when the corresponding halides were used places the correctness of equation (XXII) beyond doubt.[13]

The Wurtz and Fittig reactions can be accounted for in terms of the same initial step [equation (XXII)]. The more or less saltlike[14] alkali alkyls, which may also be formed from metal and

[12] (a) HARTEL and POLANYI, *Z. physik. Chem.*, **B11**, 97 (1930).   (b) HARTEL, MEER, and POLANYI, *ibid.*, **B19**, 139 (1932).

[13] HORN, POLANYI, and STYLE, *Z. physik. Chem.*, **B23**, 291 (1933).   HORN and POLANYI, *ibid.*, **B25**, 151 (1934).

[14] SCHLENK and MARCUS, *Ber.*, **47**, 1664 (1914); SCHLENK and HOLTZ, **50**, 262 (1917). HEIN, PETZSCHNER, WAGLER, and SEGITZ, *Z. anorg. allgem. Chem.*, **141**, 161 (1924).
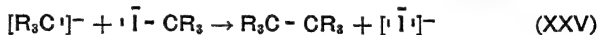
alkyl halide,[15] must result from a reaction of metal with radical, *e.g.*,

$$Na\cdot + \cdot CR_3 \rightarrow [Na]^+[\cdot CR_3]^-$$ (XXIII)
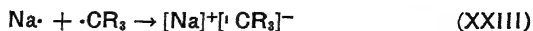
The synthetic product may result from polymerization of the radical

$$R_3C\cdot + \cdot CR_3 \rightarrow R_3C\text{-}CR_3$$ (XXIV)

or from a nucleophilic attack of the carbanion on the alkyl halide

$$[R_3C\cdot]^- + \cdot \bar{I}\text{-}CR_3 \rightarrow R_3C\text{-}CR_3 + [\cdot \bar{I}\cdot]^-$$ (XXV)

These syntheses are far from clean, and the by-products are consistent with the mechanisms suggested. The action of sodium on chlorbenzene yields only 20 per cent of biphenyl but much benzene, *o*-diphenylbenzene, and triphenylene, $(C_6H_4)_3$.[16] These are the products to be expected from a dismutation of the phenyl radical

(XXVI)
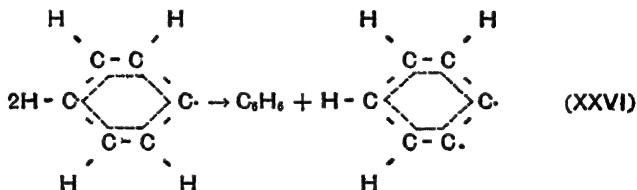
Similarly, the action of sodium on *n*-amyl chloride yields considerable amounts of $C_5H_{10}Na_2$ as well as $C_5H_{11}Na$. This is demonstrated by the formation of sodium butylmalonate as well as sodium caproate upon treatment with carbon dioxide.[15] The necessary dismutation must occur at the radical stage of the reaction since sodium amyl cannot be converted to the disodium compound.

The formation of the Grignard reagent proceeds no doubt by way of radical and carbanion in the same way as in reactions (XXII) and (XXIII), but the carbanion enters into covalent combination with the magnesium. Although the Grignard reagent does yield conducting solutions in ether,[17] transference

[15] (*a*) MORTON, LEFEVRE, and HECHENBLEIKNER, *J. Am. Chem. Soc.*, **58**, 754 (1936). (*b*) MORTON and HECHENBLEIKNER, *ibid.*, **58**, 1697 (1936).

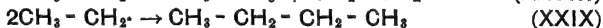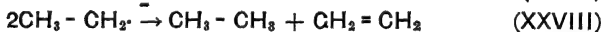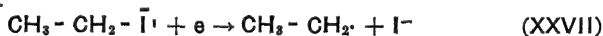[16] BACHMANN and CLARKE, *J. Am. Chem. Soc.*, **49**, 2089 (1927).

[17] (*a*) NELSON and EVANS, *J. Am. Chem. Soc.*, **39**, 82 (1917). (*b*) KONDYREW, *Ber.*, **58B**, 459 (1925). KONDYREW and MANOYEW, *ibid.*, **58B**, 464 (1925). (*c*) EVANS and LEE, *J. Am. Chem. Soc.*, **56**, 654 (1934).

experiments[17c] show a net migration of magnesium toward the anode. This requires the formulation of the reagent as the magnesium salt of some such complex ion as (F)

$$
\left[
\begin{array}{c}
\cdot\bar{B}r\cdot \\
| \\
R - Mg - R \\
| \\
\cdot\bar{B}r\cdot
\end{array}
\right]^{-}
$$
(F)
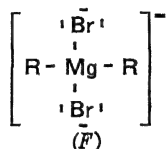
The anodic products are those to be expected from the oxidation of the carbanion to a radical (page 381), and the useful reactions of the reagent are those of a carbanion (page 329). Whether these various reactions occur after, simultaneously with, or before the separation of the organic residue from the magnesium is not known.

The correctness of these mechanisms, which attribute to the sodium or magnesium the function of a source of electrons, is verified by the fact that both Wurtz and Grignard reactions can be carried out by using an inert metal with an externally imposed negative potential instead of sodium or magnesium. Thus the electrolytic reduction of benzyl chloride[18] or ethyl iodide[19] in alcoholic medium yields appreciable proportions of dibenzyl and butane, respectively. As much as 30 per cent butane and up to 40 per cent ethylene are found with ethyl iodide. The products may be attributed to the reactions

$$
CH_3 - CH_2 - \bar{I}\cdot + e \rightarrow CH_3 - CH_2\cdot + I^- \qquad \text{(XXVII)}
$$
$$
2CH_3 - CH_2\cdot \rightarrow CH_3 - CH_3 + CH_2 = CH_2 \qquad \text{(XXVIII)}
$$
$$
2CH_3 - CH_2\cdot \rightarrow CH_3 - CH_2 - CH_2 - CH_3 \qquad \text{(XXIX)}
$$

The electrolytic Grignard reaction is obtained by the electrolysis of a mixture of benzaldehyde and ethyl iodide made conducting by tetraethylammonium iodide.[20] This yields at the cathode
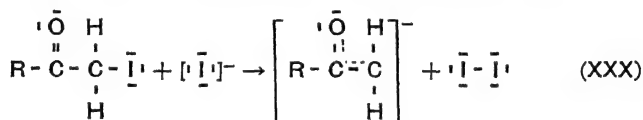
(G)   (H)
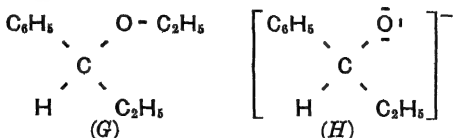
[18] MATHES, Dis., Munich, 1904.

[19] PLUMP and HAMMETT, *Trans. Electrochem. Soc.*, **78**, 523 (1938).

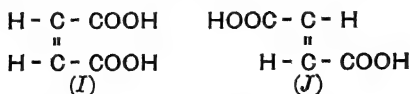[20] NELSON and COLLINS, *J. Am. Chem. Soc.*, **46**, 2256 (1924).

isolable amounts of the ethyl ether (G) of the carbinol which would have been formed had the aldehyde reacted with ethyl-magnesium iodide. The reaction course can hardly be any other than the electrolytic formation of the carbanion $C_2H_5^-$, the addition of which to the carbonyl group yields the alcoholate ion H, the reaction of which with ethyl iodide according to equation (XVII) leads to (G). The large amounts of ethylene, hydrobenzoin, unsymmetrical diphenylethylene glycol, ethyl benzoate, and stilbene also produced can be accounted for as resulting from the reactions of ethyl radicals formed according to reaction (XXVII) or from electrolytic reduction of benzaldehyde.

Nucleophilic Displacements on Halogen: Addition of Halogen to Olefins.—The reduction of a halogen compound by halide ion may be classified as a nucleophilic displacement on halogen

$$R-\overset{\overset{\cdot\bar{O}}{\|}}{\underset{\underset{H}{|}}{C}}-\overset{H}{\underset{|}{C}}-\bar{\underline{I}}\cdot + [\cdot\bar{\underline{I}}\cdot]^- \rightarrow \left[R-\overset{\overset{\cdot\bar{O}}{|}}{C}\!=\!\overset{H}{\underset{\underset{H}{|}}{C}}\right]^- + \cdot\bar{\underline{I}}-\bar{\underline{I}}\cdot \qquad (XXX)$$

The mechanism is strongly supported by the fact that the reaction goes easily only when the negative ion is stabilized by resonance as in the case shown.[21]

It requires a more violent break with tradition to recognize a similar process in the addition of halogen to the olefinic double bond, for which the classical picture involves the simultaneous addition of the two atoms of the halogen molecule to the unsaturated carbon atoms. This mechanism was, however, completely exploded by the discovery[22] that the addition occurs predominantly in what is called the *trans* configuration. For instance, the addition of bromine to maleic acid yields almost exclusively racemic dibromsuccinic acid; when added to fumaric acid the product is chiefly mesodibromsuccinic acid. If the two
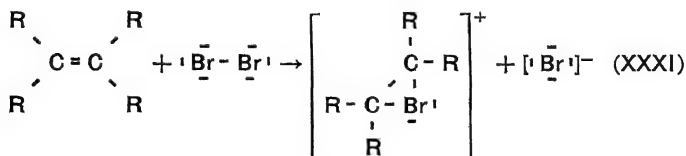
$$\begin{array}{ll} H-\overset{\|}{\underset{|}{C}}-COOH & HOOC-\overset{\|}{\underset{|}{C}}-H \\ H-C-COOH & H-C-COOH \\ \quad (I) & \quad (J) \end{array}$$

[21] Kröhnke and Timmler, *Ber.*, **69B**, 614 (1936).

[22] McKenzie, *Proc. Chem. Soc.*, **27**, 150 (1911); *J. Chem. Soc.*, **101**, 1196 (1912). Holmberg, *C. A.*, **6**, 2072 (1912). Frankland, *J. Chem. Soc.*, **101**, 673 (1912).

atoms of a bromine molecule added simultaneously to the ethylene carbons of maleic acid (*I*), they would add to the same side, either in front or in back of the plane of the diagram. The two halves of the dibromsuccinic molecule would then be mirror images, and the substance would be the internally compensated meso form. The same process, called a *cis* addition, applied to fumaric acid (*J*) would lead to a racemic mixture of optically active forms. The configurations of maleic and fumaric acids are known beyond question from both chemical and physical evidence, those of the dibromsuccinic acids are proven by resolution of the racemic substance. The actual addition is, therefore, *trans* and requires that the two bromines add one in front, one behind the diagram. This is inconceivable so long as the two atoms remain united in a bromine molecule; the process must, therefore, take place in at least two steps.

That these steps involve ionic intermediates when the reaction occurs in polar solvents appears from the following evidence. When maleate or fumarate ion reacts with bromine in aqueous solution, a bromhydrine of the composition HOOC—CHBr—CHOH—COOH is formed along with dibromsuccinic acid, but the presence in the solution of a high concentration of bromide ion inhibits its formation.[23] Further, much chlorbromsuccinic acid is formed when a high concentration of chloride ion is present. In the reaction of ethylene with bromine or iodine in aqueous solution, the addition of sodium chloride leads to the formation of chlorbrom and chloriodo ethanes, and Br—CH_2—CH_2—NO_3 is formed by the action of bromine in the presence of a high concentration of nitrate ion.[24] All these effects are accounted for by the hypothesis that the initial step is the process[24,25]
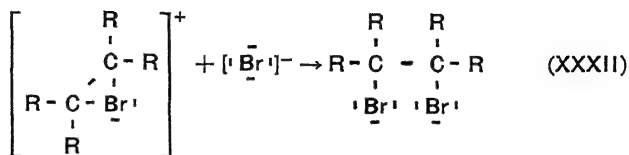
$$\begin{matrix} R & & R \\ & C = C & \end{matrix} + \text{'}\bar{Br}\text{-}\bar{Br}\text{'} \rightarrow \left[\begin{matrix} & R \\ & | \\ & C\text{-}R \\ R\text{-}C\text{-}Br\text{'} \\ & | \\ & R \end{matrix} \right]^+ + [\text{'}\bar{Br}\text{'}]^- \quad (XXXI)$$

[23] TERRY and EICHELBERGER, *J. Am. Chem. Soc.*, **47**, 1067 (1925).
[24] FRANCIS, *J. Am. Chem. Soc.*, **47**, 2340 (1925).
[25] ROBERTS and KIMBALL, *J. Am. Chem. Soc.*, **59**, 947 (1937).

The final products are then formed by the nucleophilic attack on the positive ion of bromide, chloride, or nitrate ions or of hydroxyl ion or water, *e.g.*,

$$
\left[
\begin{array}{c}
R \\
| \\
C - R \\
\diagup \; | \\
R - C - Br\, | \\
| \quad \underline{\;} \\
R
\end{array}
\right]^{+}
+ [\,|\,\underline{Br}\,|\,]^{-} \rightarrow
\begin{array}{cc}
R & R \\
| & | \\
R - C & - \; C - R \\
| & | \\
|\,\underline{Br}\,| & |\,\underline{Br}\,|
\end{array}
\qquad \text{(XXXII)}
$$

The three-ring structure of the intermediate[25] is required by the stereochemical specificity of the addition reactions. If the bromine were attached to one carbon only, there would be free rotation about the carbon-carbon link and maleic and fumaric acids must yield the same product or mixture of products. It is further inherently improbable that a carbon atom carrying only six valence electrons should be capable of existence in the close vicinity of the unshared electrons of the bromine.

The addition of bromine to stilbene in methanol solution has been examined in an admirably critical fashion.[26] Two products (*K*) and (*L*) are formed.

$$
\underset{(K)}{C_6H_5 - CHBr - CHBrC_6H_5} \qquad \underset{(L)}{C_6H_5 - CHBr - CHOCH_3 - C_6H_5}
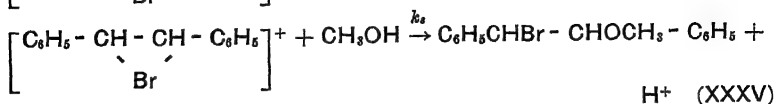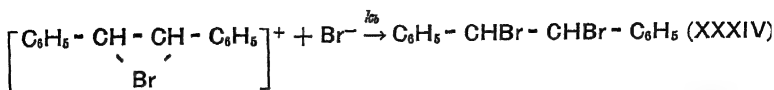$$
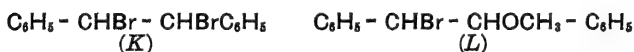
The possibility that the latter might result from the direct addition of CH_3OBr is disposed of by the kinetics, the rate being first order in stilbene and independent of the acidity of the solution. The equation for the formation of methyl hypobromite is

$$
Br_2 + 2CH_3OH \rightarrow CH_3OBr + Br^- + CH_3OH_2^+ \qquad \text{(XXXIII)}
$$
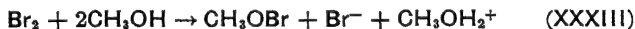
Were this rate determining, the bromine addition rate would be independent of the concentration of stilbene; if the addition of the hypobromite to stilbene were rate determining, the rate of the addition would be proportional to the concentration of the hypobromite and would vary inversely as the concentration of the solvated hydrogen ion $CH_3OH_2^+$.

The relative amounts of the substances (*K*) and (*L*) in the reaction product vary with varying concentration of bromide ion in a way that is consistent with the assumption that the positively charged intermediate may react in two ways

[26] BARTLETT and TARBELL, *J. Am. Chem. Soc.*, **58**, 466 (1936).

$$\left[C_6H_5\text{-}CH\text{-}CH\text{-}C_6H_5 \atop Br \right]^+ + Br^- \xrightarrow{k_b} C_6H_5\text{-}CHBr\text{-}CHBr\text{-}C_6H_5 \quad (XXXIV)$$

$$\left[C_6H_5\text{-}CH\text{-}CH\text{-}C_6H_5 \atop Br \right]^+ + CH_3OH \xrightarrow{k_s} C_6H_5CHBr\text{-}CHOCH_3\text{-}C_6H_5 +$$

$$H^+ \quad (XXXV)$$

The fraction x of methoxybromide formed must then vary according to

$$x = \frac{k_s}{k_s + k_b[Br^-]} \quad (1)$$

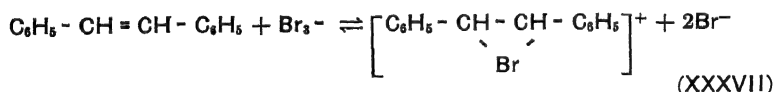A comparison of observed and calculated values of x is given in Table I.

TABLE I.—COMPOSITION OF REACTION PRODUCT IN THE STILBENE-BROMINE REACTION[26]

$[Br^-]$	x (calc.)	x (obs.)
0.200	0.812	0.821, 0.838
0.193	0.816	0.813
0.100	0.897	0.870, 0.907

The total rate of reaction of stilbene is decreased by the addition of bromide ion in a way that can be quantitatively accounted for on the basis that the tribromide ion known to be present by virtue of the equilibrium

$$Br_2 + Br^- \rightleftharpoons Br_3^- \quad (XXXVI)$$

reacts

$$C_6H_5\text{-}CH=CH\text{-}C_6H_5 + Br_3^- \rightleftharpoons \left[C_6H_5\text{-}CH\text{-}CH\text{-}C_6H_5 \atop Br \right]^+ + 2Br^-$$
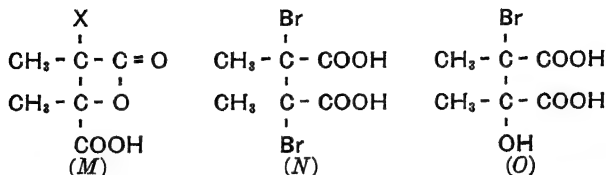
$$(XXXVII)$$

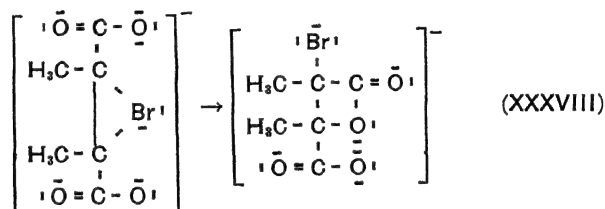at a rate 100 times slower than does bromine.

The two-step mechanism of the halogen addition is further verified by experiments with dimethylmaleate and dimethyl-fumarate ions.[27] Each of these reacts with aqueous bromine or chlorine to give as a sole product one of two stereoisomeric lactones of structure (M) ($X = Cl$ or Br). Under the prevailing

[27] TARBELL and BARTLETT, *J. Am. Chem. Soc.*, **59**, 407 (1937).

conditions, neither the dibrom compound (N) nor the brom-

$$
\begin{array}{ccc}
\quad\text{X} & \quad\text{Br} & \quad\text{Br} \\
\quad| & \quad| & \quad| \\
\text{CH}_3\text{-}\text{C}\text{-}\text{C}=\text{O} & \text{CH}_3\text{-}\text{C}\text{-}\text{COOH} & \text{CH}_3\text{-}\text{C}\text{-}\text{COOH} \\
\quad| & & \\
\text{CH}_3\text{-}\text{C}\text{-}\text{O} & \text{CH}_3\ \ \text{C}\text{-}\text{COOH} & \text{CH}_3\text{-}\text{C}\text{-}\text{COOH} \\
\quad| & \quad| & \quad| \\
\quad\text{COOH} & \quad\text{Br} & \quad\text{OH} \\
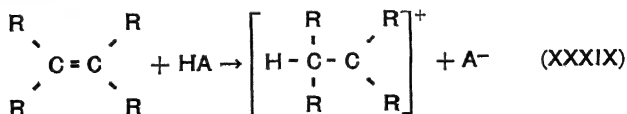\quad(M) & \quad(N) & \quad(O)
\end{array}
$$

hydrine (O) is converted to the lactone; hence, neither can be an intermediate in its formation. The lactone is not, therefore, formed by way of addition either of Br_2 or HOBr to the double bond; it may be easily produced by an internal nucleophilic displacement from the three-ring intermediate

$$
\begin{bmatrix}
\text{O} = \text{C} - \text{O} \\
\text{H}_3\text{C} - \text{C} \\
\qquad\qquad \text{Br} \\
\text{H}_3\text{C} - \text{C} \\
\text{O} = \text{C} - \text{O}
\end{bmatrix}^{-}
\rightarrow
\begin{bmatrix}
\qquad \text{Br} \\
\text{H}_3\text{C} - \text{C} - \text{C} = \text{O} \\
\text{H}_3\text{C} - \text{C} - \text{O} \\
\text{O} = \text{C} - \text{O}
\end{bmatrix}^{-}
\qquad \text{(XXXVIII)}
$$

There is one known exception to the rule of *trans* addition of halogen in polar solvents: maleate ion yields the same product as fumarate ion, *viz.*, mesodibromsuccinate ion.[28] This reaction may be accounted for[25] on the basis that the electrostatic repulsion between the carboxylate ion groups is sufficient to rupture the three-membered ring and rotate the two halves of the molecule into the fumaroid configuration in which the charges are as widely separated as possible.
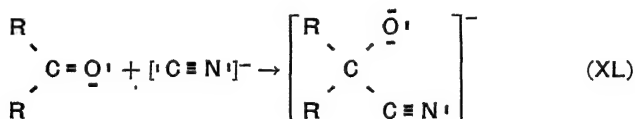
Other Addition Reactions.—The halogen addition is typical of the reactions of the olefinic double bond. In polar solvents like water or methanol the intermediates are ionic, and the ethylenic compound acts as a nucleophilic reagent furnishing both of the electrons necessary for a new bond. Thus olefins react with acids (page 292)

$$
\begin{array}{c}
\text{R}\qquad\text{R} \\
\diagdown\ \diagup \\
\quad\text{C}=\text{C} \quad + \text{HA} \rightarrow \\
\diagup\ \diagdown \\
\text{R}\qquad\text{R}
\end{array}
\begin{bmatrix}
\quad\text{R}\qquad\text{R} \\
\quad| \quad\diagup \\
\text{H}-\text{C}-\text{C} \\
\quad| \quad\diagdown \\
\quad\text{R}\qquad\text{R}
\end{bmatrix}^{+}
+ \text{A}^{-}
\qquad \text{(XXXIX)}
$$

[28] KUHN and WAGNER-JAUREGG, *Ber.*, **61**, 519 (1928).

forming carbonium ions, which are the intermediates in a wide variety of reactions. In the gas phase or in solvents of low polarity, on' the other hand, their reactions are generally complicated chain processes with atom or radical intermediates (page 373).

The carbonyl group has a pronounced polarity, the oxygen being relatively negative, the carbon positive. When substances containing this unsaturated group react with acids, the proton goes to the oxygen (page 59), whereas the typical synthetic reactions of the group depend upon the electrophilic property of the carbon. A classical example is the cyanhydrine reaction, the final result of which is the addition of an HCN molecule to the carbonyl double bond. Yet acetone and HCN have a half time of reaction of 3 to 4 hr., although the reaction of acetone and cyanide ion under the same conditions is effectively complete in 2 min.[29] The slow reaction with HCN probably depends upon the presence of small amounts of cyanide ion. The only reasonable mechanism is

$$
\begin{array}{c}
\text{R} \\
\diagdown \\
\text{C} = \underset{\cdot}{\underline{\text{O}}}\,\text{'} + [\,\text{'}\,\text{C} \equiv \text{N}\,\text{'}\,]^{-} \rightarrow \\
\diagup \\
\text{R}
\end{array}
\left[
\begin{array}{cc}
\text{R} & \overset{\cdot\cdot}{\underline{\text{O}}}\,\text{'} \\
\diagdown & \diagup{}_{\cdot}^{-} \\
 & \text{C} \\
\diagup & \diagdown \\
\text{R} & \text{C} \equiv \text{N}\,\text{'}
\end{array}
\right]^{-}
\qquad \text{(XL)}
$$

followed by the transfer of a proton to the oxygen from a solvent molecule or from HCN or some other acid.

The Validity of the Classification: Structural Effects.—The discussion of these examples of the displacement reaction has involved a classification and an accompanying nomenclature, which would be formal and trivial if they did not permit the correlation of otherwise unrelated phenomena. But this classification does permit the qualitative prediction of the effect of structure on reactivity to an extent that gives it utility and therefore validity. Table II contains data on the effect of the structure of the alkyl group on the rates of a number of reactions.

The first nine reactions are nucleophilic displacements on carbon, the displacing agent being in some cases a negative ion, in others a neutral molecule with a lone pair. The reactions

[29] LAPWORTH, *J. Chem. Soc.*, **83**, 995 (1903). JONES, *ibid.*, **105**, 1560 (1914).

of this group have the following features in common. The rate decreases in the order methyl, ethyl, *i*-propyl, *t*-butyl, *i.e.*, with substitution of methyl for α-hydrogen. It also decreases with substitution of methyl for β-hydrogen, *i.e.*, in the order ethyl, *n*-propyl, *i*-butyl. In the case of the final member of the latter series, β-trimethylethyl or neopentyl, no reactions of this sort have been observed under the most strenuous conditions, such as the action of alcoholic potassium hydroxide at 100° for 20 hr. or that of potassium acetate in alcohol at 125° for 30 hr.[30] The rate is only slightly affected by substitution of methyl for hydrogen in the γ-position or at a position more widely removed from the reacting group. Olefinic unsaturation of the α-carbon suppresses the reactions entirely as in phenyl and vinyl halides, whereas unsaturation of the β-carbon in allyl and benzyl halides increases the rate largely.

Reactions (10) to (14) involve an electrophilic displacement on halogen or oxygen. This is obviously the case with reaction (10), it is almost certainly so with the others. The reactions differ strikingly from those of the first group in the effect of the substitution of methyl for α-hydrogen. The rate increases in the order ethyl, *i*-propyl, *t*-butyl, especially in the last step.[31] The irregularity in the position of methyl may be due to a failure to isolate the reaction desired compared with a competing nucleophilic displacement on carbon which leads to the same product (page 170). With respect to the substitution of methyl for β-hydrogen and to the effect of unsaturation these reactions are, however, similar to those of the first group. Neopentyl,[30] phenyl, and vinyl halides are completely unreactive toward silver ion.

Reaction (15) is a radical displacement on halogen. It resembles the reactions of the second group in the effect of substitution on the α-carbon but is unlike those of either the first or second group in that of substitution on the β-carbon and of unsaturation of the α-carbon, since the relative rates for vinyl chloride and chlorbenzene are 0.9 and 2.0. These structural

[30] WHITMORE and FLEMING, *J. Am. Chem. Soc.*, **55**, 4161 (1933).

[31] The same structural effect appears in the reaction of alkyl bromides with the electrophilic $HgBr_2$. READ and TAYLOR, *J. Chem. Soc.*, 1872 (1939).

TABLE II.—Effect of Structure of Alkyl Group on Reactivity

Reaction	Relative rate								
R =	CH_3	C_2H_5	i-C_3H_7	t-C_4H_9	n-C_3H_7	i-C_4H_9	n-C_4H_9	Allyl	Benzyl
1. $RCl + I^- \rightarrow RI + Cl^-$	......	1.	0.0077	0.0092	0.53	......	0 52	41.	95.
2. $RI + C_2H_5O^- \rightarrow C_2H_5OR + I^-$	1.	0 222	0.0766	......	0.0857	0 0318	0.0799	4.08	......
3. $RI + C_2H_5CH_2O^- \rightarrow C_2H_5CH_2OR + I^-$	1.	0.091	0.0210	......	0 0354	0.0329	0.0254	......	......
4. $RI + $ 1-phenyl-3-thiourazolate ion	1.	0.0439	0.0031	0.0001	0.028	0.00118	0.0297	......	......
5. $RI + $ acetacetic ester anion	1.	0.1	0 01	v.sl.	0.03	0 005	......	>4	ca 13
6. $RI + N(C_2H_5)_3 \rightarrow (C_2H_5)_3NR^+ + I^-$	1.	0.0087	0.0017	v.sl.	0.0017	0.00027	0.0012	......	......
7. $RI + C_6H_5N(CH_3)_2 \rightarrow C_6H_5N(CH_3)_2R^+ + I^-$ (a)	1.	0.0057	......	......	0.0208	......	......	7.55	ca 20
8. $RI + S_2O_3^- \rightarrow RS_2O_3^- + I^-$ (a)	1.	0.059	0.061	......	......	......	......	......	......
9. $RI + S_2O_3^- \rightarrow RS_2O_3^- + I^-$ (b)	......	......	......	......	1.	......	0.734	120	v.f.
10. $RI + Ag^+ \rightarrow R^+ + AgI$	......	2.35	ca 90	......	1.05	0.148	......	......	......
11. $ROH + HBr \rightarrow RBr + H_2O$	1.	0.178	0.409	v.f.	0.154	......	0.160	......	......
12. $CH_3COOR + HBr \rightarrow RBr + CH_3COOH$	1.	0.172	0.169	2×10^4	0.14	0.015	0.092	......	21.7
13. $ROH + C_6H_6 \rightarrow C_6H_5R + H_2O$	None	Dif.	Easy	......	......	Easy	......	......	Easy
14. $RBr + H_2O \rightarrow ROH + HBr$	1.	0.413	0.641	2700.	......	......	......	......	......
15. $RCl + Na \rightarrow R + NaCl$	1.	1.4	3.0	6.7	2.3	2.9	3.0	40.	10^4

v.sl. = too slow for measurement; v.f. = too fast for measurement; none, difficult and easy are in terms of synthetic procedures.

Notes on the Reactions of Table II

1. Alkyl chloride and potassium iodide in acetone at 60°c, in some cases extrapolated from data at lower temperatures. Absolute value of second-order constant of ethyl chloride 5.44×10^{-5} (l./mole sec.)[32]

2. Alkyl iodide and sodium phenolate in ethanol at 42.5°c.[33] Second-order constant for methyl iodide 1.012×10^{-3}.

3. Alkyl iodide and sodium benzyloxide in ethanol at 30°c.[34] Second-order constant for methyl iodide 2.63×10^{-3}.

4. Alkyl iodide and sodium salt of 1-phenyl-3-thiourazol in 50 per cent ethanol at 25°c.[35]

5. Alkyl iodide and sodium acetacetic ester in ethanol at the boiling point. Very rough measurements of relative rates.[36]

6. Alkyl iodide and triethylamine in acetone at 100°c.[37]

7. Alkyl iodide and dimethylaniline in ethanol at 40°c.[38] Second-order constant for methyl iodide 1.31×10^{-4}.

8. Alkyl iodide and sodium thiosulfate in water at 25°c. Value for benzyl iodide estimated from that for benzyl chloride. Second-order constant for methyl iodide 0.0142.[39]

9. Same as 8, but in a 5:3 by volume ethanol-water mixture at 35°c.[39] Second-order constant for n-propyl iodide 0.93×10^{-3}.

10. Alkyl iodide and silver nitrate in ethanol at 25.4°c.[40] The final products are alkyl nitrate and alcohol, with in some cases olefin. Second-order constant for methyl iodide 1.558×10^{-5}.

11. Alcohol and HBr with phenol as solvent at 80.3°c.[41] Second-order constant for methanol 2.97×10^{-4}.

12. Alkyl acetate and HBr in glacial acetic acid at 18 to 21°c.[42]

13. Condensation of alcohol with benzene by 70 to 80 per cent H_2SO_4.[7]

14. Solvolytic hydrolysis of alkyl bromide in 80 per cent ethanol at 25°c.[43] First-order constant for methyl bromide 1.222×10^{-7}.

15. Gas-phase reaction of alkyl chloride and sodium.[12b]

[32] CONANT and KIRNER, *J. Am. Chem. Soc.*, **46**, 233 (1924); CONANT and HUSSEY, *ibid.*, **47**, 476 (1925); CONANT, KIRNER, and HUSSEY, *ibid.*, **47**, 488 (1925).

[33] SEGALLER, *J. Chem. Soc.*, **103**, 1154; 1421 (1913); **105**, 106; 113 (1914).

[34] HAYWOOD, *J. Chem. Soc.*, **121**, 1904 (1922).

[35] ACREE and SHADINGER, *Am. Chem. J.*, **39**, 226 (1908).

[36] WISLICENUS, *Ann.*, **212**, 239 (1882).

[37] MENSCHUTKIN, *Z. physik. Chem.*, **5**, 589 (1890).

[38] PRESTON and JONES, *J. Chem. Soc.*, **101**, 1930 (1912).

[39] SLATOR and TWISS, *J. Chem. Soc.*, **95**, 93 (1909).

[40] BURKE and DONNAN, *J. Chem. Soc.*, **85**, 555 (1904).

[41] BENNETT and REYNOLDS, *J. Chem. Soc.*, 131 (1935).

[42] TRONOV and SSIBGATULLIN, *Ber.*, **62B**, 2850 (1929).

[43] TAYLOR, *J. Chem. Soc.*, 992 (1937).

effects are those which are qualitatively well known in the Wurtz and Grignard reactions, both of which succeed as well with phenyl, vinyl, and neopentyl halides as with any others.

Without going further into the problem of the effect of structure on reactivity, one may derive two useful generalizations from these data. (1) *Reactions that are differently affected by variations in the structure of reactant belong to different reaction types and have different mechanisms and different driving forces.* (2) *No single order of "electronegativity" or of "Haftfestigkeit" can apply to reactions of different types.*

CHAPTER VI

STEREOCHEMISTRY OF THE DISPLACEMENT REACTION

Retention and Inversion of Configuration.—The Polanyi picture of the displacement reaction has had a most important influence on the development of stereochemical theory because it offers so satisfactory a mechanism for the phenomena of the Walden inversion. The experimental crux of Walden's discovery is the possibility of carrying out a cycle of reactions by which an optically active substance is converted to its isomer of
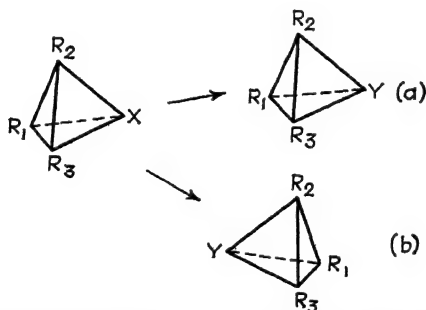
Fig. VI-1.—Retention (a) and inversion (b) of configuration in displacement reactions.

opposite rotation. It is, for instance, possible to convert dextrorotatory chlorsuccinic acid to malic acid and then to change this to levorotatory chlorsuccinic acid. The existence of such cycles proves that a displacement reaction *may* be accompanied by inversion of configuration in the sense of Fig. 1*b*. If as in Fig. 1*a* the displacement of a group X attached to carbon by the group Y leaves the relative positions of the central carbon atom and the groups R_1, R_2, and R_3 unaltered, the reaction is said to proceed with *retention of configuration;* if, as in Fig. 1*b*, the product is the mirror image of that produced with retention, the reaction is said to go with *inversion of configuration.*

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At least once, but possibly any odd number of times, during the cycle a displacement has, therefore, taken place with inversion; an even number of inversions restores the original configuration. Beyond this it is impossible to go on the basis of the inversion alone, because the cycle necessarily requires a number of displacements, a number that is not even known a priori because any one of the reactions which are recognizable in terms of isolable products may consist of a series of displacements with unstable intermediates.

This situation produces two important and insistent problems. The structural theory of organic chemistry is incomplete so long as the relative configurations of synthetically related substances such as the chlorsuccinic acids and the malic acids remain unknown. And preparative chemistry is in an unsatisfactory state until it is possible by known and predictable methods to prepare a product of desired configuration from a given reactant. The first problem should, in principle, be soluble by methods of optical and structural theory; it is not at present soluble in practice on this basis, but considerable progress has been made from the study of reaction mechanisms. The second problem is in any case a problem in mechanisms, toward the solution of which the way now seems clearly laid out.

Theoretical Approaches.—The displacement process discussed in Chap. V is at least consistent with the existence of inversions of configuration. When the symbols A, B, and C of the type reaction

$$A + BC \rightarrow AB + C \tag{I}$$

represent single atoms, atom A is constrained to approach the BC molecule along the line of centers, keeping as far as possible from the C atom. If the same principle applies to displacements on an asymmetric carbon atom such as

$$[\cdot \bar{\text{I}} \cdot]^- + \text{R}_2 - \overset{\text{R}_1}{\underset{\text{R}_3}{\text{C}}} - \bar{\text{C}}\text{l} \cdot \rightarrow \cdot \bar{\text{I}} - \overset{\text{R}_1}{\underset{\text{R}_3}{\text{C}}} - \text{R}_2 + [\cdot \bar{\text{C}}\text{l} \cdot]^- \tag{II}$$
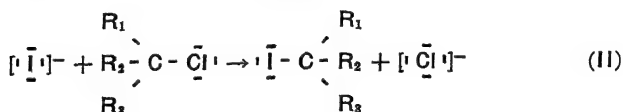
the iodide ion must approach the $CR_1R_2R_3Cl$ tetrahedron in the direction of the center of the face opposite the vertex occupied by the chlorine atom. As it approaches, the carbon-chlorine

link must stretch, and, in addition, the R's must recede from their original position. In the transition state they will lie in a plane with the central carbon atom or nearly so, and in the final product they will have continued their motion so that they lie on the opposite side of the carbon. Meanwhile, the iodine atom has become attached to the carbon on the side opposite to that originally occupied by the chlorine, which has escaped as chloride ion. The process is symbolized in Fig. 2, in which a is the original state, b the transition state, and c the final state. The behavior of the three C—R linkages is like that of the ribs of an umbrella in a gale.

This is a possible mechanism for the inversion, the difficulty is to determine if it is the only possible kind of displacement reaction. The theory demands only that the entering iodide ion approach in such a way as to keep the repulsions due to groups or atoms with which it is not in the process of combining as small as possible. Since it is repelled by the R's as well as by chlorine, it is not obviously necessary that it keep as far from chlorine as possible at the expense of a closer approach to the other groups. If it should approach a face of the tetrahedron adjacent to the chlorine, the result would probably be retention rather than inversion of configuration.

Fig. VI-2.—Original (a), transition (b) and final (c) states in the displacement of chloride ion by iodide ion.

The field due to the dipole moment of the carbon-chlorine link would tend to orient the approaching ion away from chlorine,[1] but the ion-dipole forces are much weaker than the valence forces that control the displacement process and can hardly be very significant. In fact, inversion occurs (page 176) even when one of the R groups is the carboxylate ion group, which must repel the approaching ion more strongly than the dipole, and would tend to orient it toward a face adjacent to the chlorine.

[1] MEER and POLANYI, *Z. physik. Chem.*, **B19,** 164 (1932).

The hypothesis that the displacement is always accompanied by inversion has also been justified from pictures of the approximate electronic distribution of the carbon atom[2] and from other quantum mechanical considerations.[3] Both approaches are suggestive, but neither has been developed to the point where it might be called a proof.
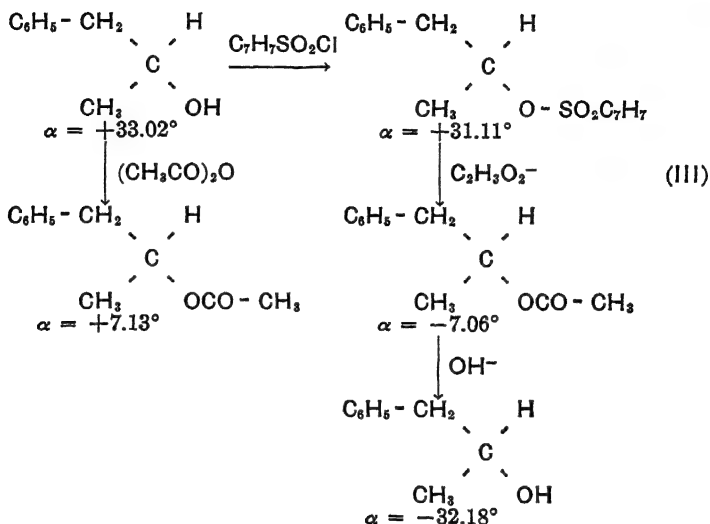
The Experimental Approach.—Experimental evidence has, however, reached a point where the principle that every displacement inverts is established with a high degree of reliability. This conclusion or indeed any definite one does not immediately emerge from the enormous amount of complicated and confusing data available. In addition to the fact that an actual cycle involves an unknown number of displacements, the racemization that frequently accompanies these reactions suggests the possibility of parallel reaction paths by which a reactant of one configuration leads to a product containing both stereoisomers. Finally, there is the unfortunate accident that the most easily available optically active compounds are the sugars, the terpenes, and the substances easily obtainable from amino acids or from lactic and malic acids. For reasons that will appear shortly, the reactions of these substances are exceptionally complex and difficult to interpret. The failure to recognize them as special cases has contributed largely to an utter and complete confusion, which leads one almost to suspect that some investigators have wished to prove that the situation is too complicated to permit any solution rather than by simplification of the problem to proceed stepwise toward one.

Reactions of Alkyl Toluenesulfonates.—A first and most important step in the direction of the necessary isolation of variables was made in a series of investigations by Kenyon, Phillips, and their coworkers. Recognizing the probability that the easily accessible substances might offer especially complicated material, they undertook and solved the difficult problem of preparing a series of optically active alcohols containing only one center of asymmetry. Working with these they soon

[2] OLSON, *J. Chem. Phys.*, **1**, 418 (1933).

[3] COWDREY, HUGHES, INGOLD, MASTERMAN, and SCOTT, *J. Chem. Soc.*, 1252 (1937).

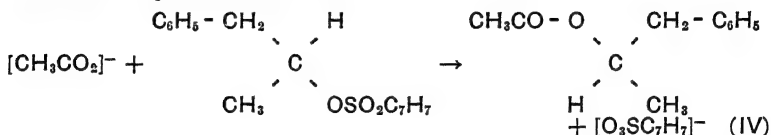found a number of clear and unambiguous cases of the following sort:[4]

$$C_6H_5 - CH_2 \quad H$$
$$\diagdown \diagup$$
$$C$$
$$\diagup \diagdown$$
$$CH_3 \quad OH \qquad \xrightarrow{\ C_7H_7SO_2Cl\ }$$
$$\alpha = +33.02°$$

$$\Big\downarrow (CH_3CO)_2O$$

$$C_6H_5 - CH_2 \quad H$$
$$\diagdown \diagup$$
$$C$$
$$\diagup \diagdown$$
$$CH_3 \quad OCO - CH_3$$
$$\alpha = +7.13°$$

$$C_6H_5 - CH_2 \quad H$$
$$\diagdown \diagup$$
$$C$$
$$\diagup \diagdown$$
$$CH_3 \quad O - SO_2C_7H_7$$
$$\alpha = +31.11°$$

$$\Big\downarrow C_2H_3O_2{}^-$$

$$C_6H_5 - CH_2 \quad H$$
$$\diagdown \diagup$$
$$C$$
$$\diagup \diagdown$$
$$CH_3 \quad OCO - CH_3$$
$$\alpha = -7.06°$$

$$\Big\downarrow OH^-$$

$$C_6H_5 - CH_2 \quad H$$
$$\diagdown \diagup$$
$$C$$
$$\diagup \diagdown$$
$$CH_3 \quad OH$$
$$\alpha = -32.18°$$

(III)

The reaction of the dextrorotatory carbinol with toluenesulfonyl chloride followed by reaction of the toluenesulfonate with acetate ion (potassium acetate in alcohol) yields a levorotatory acetate, whereas the direct acetylation of the dextrorotatory alcohol yields a dextrorotatory acetate. All the reactions may be carried out with high yields, and the magnitude of the rotation of the two acetates is nearly the same.

The step involving the rotation may be definitely placed by the following process of elimination. It cannot be the reaction of carbinol with sulfonyl chloride because this does not break any of the linkages of the asymmetric carbon. No inversion can conceivably occur unless one of these is broken and replaced by a new link in the opposite configuration. A displacement at another point in the molecule, in this case the displacement of hydrogen attached to oxygen by the toluenesulfonyl group, cannot invert. The same reasoning applies probably, although not so certainly, to the acetylation of the carbinol; the conclusion is proven by the fact that the dextrorotatory acetate obtained by

[4] PHILLIPS, *J. Chem. Soc.*, **123**, 44 (1923).

acetylation of the dextro alcohol yields dextro alcohol on alkaline saponification. It is now known beyond question that the saponification of simple carboxylic esters leaves the carbon-oxygen linkages of the alcohol component untouched and so cannot invert the configuration of the carbinol carbon (page 354). Consequently, the inversion in reaction system (III) can have occurred only in the reaction

$$[CH_3CO_2]^- + \quad \begin{array}{c} C_6H_5-CH_2 \quad\quad H \\ C \\ CH_3 \quad\quad OSO_2C_7H_7 \end{array} \quad \rightarrow \quad \begin{array}{c} CH_3CO-O \quad\quad CH_2-C_6H_5 \\ C \\ H \quad\quad CH_3 \\ + [O_3SC_7H_7]^- \quad (IV) \end{array}$$

This is indeed the kind of simple displacement process for which an inversion can be visualized in terms of the mechanism of Fig. 2. The toluenesulfonate ion plays the role of the chloride ion in that diagram, the acetate ion that of the iodide ion. Similar experiments have shown that the same sort of phenomena appear when valerates instead of acetates are used. A similar cycle demonstrates that the displacement of toluenesulfonate ion by ethylate ion inverts the configuration of the carbinol carbon. The reaction of the carbinol of equation (III) with ethyl bromide in the presence of potassium hydroxide is a nucleophilic displacement of bromide ion by the alcoholate ion of the carbinol; it does not affect the linkages of the asymmetric carbon and cannot invert its configuration. The ethyl ether of the carbinol thus obtained has a rotation of $+23.50°$. On the other hand, the reaction of the toluenesulfonate with ethyl alcohol in the presence of potassium carbonate yields an ethyl ether, the rotation of which is $-19.90°$ and must have inverted the configuration.

. Similar experiments with like results have been performed on the alcohols $C_2H_5—CHOH—CH_3$,[5] $CH_3—CHOH—COOC_2H_5$,[6] $CH_3—CHOH—CONH_2$,[7] on menthol[8] and on the isomeric 2-methylcyclohexanols.[9] With s-octanol the toluenesulfonate was prepared by oxidation of the toluenesulfinate, which was

[5] KENYON, PHILLIPS, and PITTMAN, *J. Chem. Soc.*, 1072 (1935).

[6] KENYON, PHILLIPS, and TURLEY, *J. Chem. Soc.*, **127**, 399 (1925).

[7] BEAN, KENYON, and PHILLIPS, *J. Chem. Soc.*, 303 (1936).

[8] PHILLIPS, *J. Chem. Soc.*, **127**, 2552 (1925).

[9] GOUGH, HUNTER, and KENYON, *J. Chem. Soc.*, 2052 (1926).

in turn prepared by the action of toluenesulfinic chloride on the carbinol. If the entirely reasonable assumption that neither of these reactions invert, an assumption that has been directly verified with s-butyl alcohol, is accepted, inversion is proved for the displacement reactions of the octyl toluenesulfonate with various carboxylate and alkyloxy ions.[8] In the case of two α-phenyl compounds C_6H_5—CHOH—CH_3[10] and C_6H_5CHOH—CH_2—COOH[11] the toluenesulfonates are too unstable to be isolated, but their reactions can be studied by treatment of the toluenesulfinate with hydrogen peroxide in the presence of the reagent the reaction of which with the sulfonate is to be investigated. Here also the displacement of toluenesulfonate ion by acetate, ethoxy, or butoxy ions is accompanied by inversion. There is, however, considerable racemization.

These results furnish a large and convincing body of evidence for the conclusion that the displacement of toluenesulfonate ion by a carboxylate or alkyloxy ion is invariably accompanied by inversion of configuration and suggest strongly that any nucleophilic displacement on carbon inverts.[12] The only difficulty, the racemization observed with the phenyl derivatives, has been solved by more recent kinetic investigations, which are in fact indispensable for the verification of the more general conclusion.

Racemization by Halide Ions.—Alkyl bromides are racemized by bromide ion and alkyl iodides by iodide ion at a rate that is proportional to the concentration of the halide ion.[13] The reaction is, therefore, a second-order one of halide ion with alkyl halide and can hardly be anything else than an inverting displacement of bromide ion by bromide ion or of iodide ion by iodide ion. This converts dextro-bromide to levo, levo-bromide to dextro and reaches a state of equilibrium when racemization is complete. The result does not, however, prove that all displacements invert. The displacements with inversion might conceivably be accompanied by a much larger number of displacements with retention of configuration; the end result would still be complete racemization.   •

[10] Kenyon, Phillips, and Taylor, *J. Chem. Soc.*, 173 (1933).
[11] Kenyon, Phillips, and Shutt, *J. Chem. Soc.*, 1663 (1935).
[12] Kenyon and Phillips, *Trans. Faraday Soc.*, **26**, 451 (1930).
[13] Holmberg, *J. prakt. Chem.*, **88**, [2], 553 (1913).

Various evidence for the hypothesis that the displacement necessarily inverts has been found.   Thus the rate of racemization of s-hexyl iodide by iodide ion is of the order of magnitude predicted on the basis of this hypothesis from the rates of reaction of the hexyl fluoride, the hexyl chloride, and the hexyl bromide with iodide ion.[14]   The change in rotation with time of a solution containing l-chlorsuccinic acid and bromide ion can be accounted for only if it is supposed either that practically every displacement of chloride ion by bromide ion or of bromide ion by chloride ion inverts or, much less probably, that these reactions are accompanied by retention of configuration.[15]

The Application of Radioactive Indicators.—The complete demonstration of the invariable inversion in halide-ion displacements has come through the application of radioactive indicators.[16]   The recent discovery of artificial radioactivity has made it possible to obtain an iodide ion which is identical in all its chemical properties with ordinary iodide ion, yet which by virtue of its radioactivity can be differentiated from the nonradioactive substance and quantitatively determined.   When a sample of ordinary s-octyl iodide is dissolved in acetone containing radioactive iodide ion, the octyl iodide becomes radioactive at a rate that may be determined by separating organic and inorganic iodides (by treatment with water and an immiscible organic solvent) and determining their activity.

The isotope exchange is a reversible process

$$RI + I^{*-} \underset{k_1}{\overset{k_1}{\rightleftharpoons}} RI^* + I^- \tag{V}$$

(the star designating the radioactive halogen) complicated by the decay of the short-lived radioactivity.   If k_1 is the specific rate of the exchange and k_r that of the decay, the rate equations are

$$\frac{d[RI^*]}{dt} = k_1[RI][I^{*-}] - k_1[RI^*][I^-] - k_r[RI^*] \tag{1}$$

[14] BERGMANN, POLANYI, and SZABO, *Trans. Faraday Soc.*, **32**, 843 (1936).

[15] OLSON and LONG, *J. Am. Chem. Soc.*, **56**, 1294 (1934).

[16] HUGHES, JULIUSBURGER, MASTERMAN, TOPLEY, and WEISS, *J. Chem. Soc.*, 1525 (1935).   HUGHES, JULIUSBURGER, SCOTT, TOPLEY, and WEISS, *ibid.*, 1173 (1936).   COWDREY, HUGHES, NEVELL, and WILSON, *ibid.*, 209 (1938).

$$\frac{d[I^{*-}]}{dt} = k_1[RI^*][I^-] - k_1[RI][I^{*-}] - k_r[I^{*-}] \tag{2}$$

If A represents the total concentration of alkyl iodide and B that of iodide ion, an experimentally determinable ratio γ may be defined by

$$\gamma \equiv \frac{[RI^*]/A}{[I^{*-}]/B} \tag{3}$$

From equations (1), (2), and (3) and the definitions of A and B, it follows that

$$\frac{1}{k_1}\frac{d\gamma}{dt} = B + (A - B)\gamma - A\gamma^2 \tag{4}$$

$$k_1 t = \frac{1}{A + B}\ln\frac{1 + (A/B)\gamma}{1 - \gamma} \tag{5}$$

Values of k_1 may, therefore, be calculated from measurements of γ and t.

The racemization involves the reversible reaction

$$d\text{RI} + \text{I}^- \underset{k_1}{\overset{k_1}{\rightleftharpoons}} l\text{RI} + \text{I}^- \tag{VI}$$
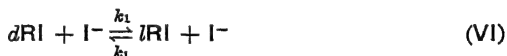
and the rate equation

$$-\frac{d[d\text{RI}]}{dt} = \frac{d[l\text{RI}]}{dt} = k_1[d\text{RI}][I^-] - k_1[l\text{RI}][I^-] \tag{6}$$

The rotation is given by (page 103)

$$\alpha = m\{[d\text{RI}] - [l\text{RI}]\} \tag{7}$$

from which

$$\frac{d\alpha}{dt} = -2k_1[I^-]\alpha \tag{8}$$

and

$$\ln\alpha_0 - \ln\alpha = 2k_1[I^-]t \tag{9}$$

If every displacement is accompanied by inversion, the k_1 derived from the exchange experiments will be identical with that from the racemization; if not the former value will be greater. The data of Table I leave, therefore, little room for doubt that a halide-halide ion displacement is always accompanied by inversion.

Nucleophilic Displacements: General Conclusions.—In view of such results as these, it is extremely probable not merely that all displacements of one ion by another invert the configuration of the carbon atom on which they occur, but that *all* nucleophilic displacements on carbon invert. The essential feature of the ionic reactions is not the fact that ions are involved, it is the presence of unshared electron pairs as shown in reaction (II). But the reactions of page 144 for the alkylation of amines or the decomposition of quaternary ammonium ions involve the same kind of nucleophilic displacement and must be expected to invert the configuration of the carbon atom on which the displacement occurs.

TABLE I.—COMPARISON OF ISOTOPE EXCHANGE AND RACEMIZATION[16]
Values of $10^4 k_1$

	s-Octyl iodide	α-Phenyl-ethyl bromide	α-Bromo-propionic acid
Exchange......................	13.6 ± 1.1	8.72 ± 0.93	5.15 ± 0.50
Racemization..................	13.1 ± 0.1	7.95 ± 0.13	5.24 ± 0.05

An Alternative Reaction Path: Attack on Halogen: Solvolytic Reactions.—The second-order reaction of hydroxyl ion with an alkyl chloride involves an attack of hydroxyl ion on carbon; the same product, the alcohol, may be obtained by the attack of mercuric ion on the chlorine of the alkyl chloride in the presence of water (page 138). A similar attack upon halogen appears to be involved in an important type of reaction that has been called *solvolytic*[17] or characterized as a "nucleophilic substitution of the first order."[18]

Thus α-phenylethyl chloride is hydrolyzed to the alcohol at a rate that is independent of the concentration of hydroxyl ion,[19] it is converted by ethyl alcohol to the ethyl ether at a rate independent of the concentration of ethoxyl ion[19] and to phenylethyl

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[17] (a) STEIGMAN and HAMMETT, *J. Am. Chem. Soc.*, **59**, 2536 (1937). (b) FARINACCI and HAMMETT, *ibid.*, **59**, 2542 (1937); **60**, 3097 (1938).

[18] HUGHES, INGOLD, and PATEL, *J. Chem. Soc.*, 526 (1933). HUGHES and INGOLD, *ibid.*, 244 (1935); *Nature*, **132**, 933 (1933).

[19] WARD, *J. Chem. Soc.*, 445, (1927).

acetate by glacial acetic acid at a rate independent of the concentration of acetate ion.[17a] Similarly, the rate of the reaction

$$(C_6H_5)_2CHN(CH_3)_3{}^+ + OH^- \rightarrow (C_6H_5)_2CHOH + N(CH_3)_3 \quad \text{(VII}$$
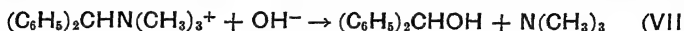
is independent of the concentration of hydroxyl ions.[18,20] In all these cases the reaction rate is independent of the concentration of the group that enters into combination with carbon, and the reaction is of the first order. The conversion of chloride to alcohol, for instance, cannot depend upon the direct displacement of chloride ion by hydroxyl ion because this would require proportionality between rate and hydroxyl-ion concentration, second-order instead of first-order kinetics.

It is a most illuminating fact that the solvents which permit this kind of reaction are precisely those, *viz.*, water, alcohols, phenols, carboxylic acids, and sulfur dioxide, which strongly favor the ionization of triphenylmethyl chloride and do so primarily by solvating the halide ion (page 54). This leads to the concept[17] of an incipient solvation of the halide ion in the transition state as the driving force of the solvolytic reaction—a hypothesis which is supported by the fact that the same metallic compounds that favor the ionization of the triphenylmethyl chloride by virtue of their affinity for halide ion also accelerate the solvolytic reaction. Thus mercuric chloride and zinc chloride materially increase the rate of conversion of α-phenylethyl chloride to its ethyl ether in alcohol solution.[21] Chloride ion in the form of lithium chloride not only yields no acceleration, it suppresses that produced by the heavy metal halides by converting them to such complexes as $HgCl_4{}^=$.

The Reaction-product Criterion.—The interpretation of the solvolytic reaction as an attack on halogen is further supported by the behavior of the system when more than one reaction product is formed: Benzhydryl chloride, $(C_6H_5)_2CHCl$, is converted to benzhydryl ethyl ether in alcohol solution by a reaction the rate of which is the same in acid, neutral, and alkaline solutions and is, therefore, independent of the concentration of the ethylate ion.[22] Upon the addition of water, the rate increases

[20] HUGHES and INGOLD, *J. Chem. Soc.*, 69 (1933).

[21] BODENDORF and BÖHME, *Ann.*, **516**, 1 (1935).

[22] WARD, *J. Chem. Soc.*, 2285 (1927).

linearly as shown in Fig. 3.[17b,22,23]   The effect is so large and occurs at concentrations of water so small that it cannot conceivably be attributed to a general solvent effect such as a change in the dielectric constant of the medium; indeed the effect produced by nitrobenzene, which likewise increases the dielectric constant, is in the opposite direction.[17b] Clearly, a first-order reaction of benzhydryl chloride with water is superimposed on the reaction with alcohol.   Yet the reaction product remains to a preponderant extent benzhydryl ethyl ether rather than the benzhydrol which one might expect to result from the reaction of the chloride with water.   Table II shows the proportions of benzhydrol actually found in the reaction product together with those to be expected if the reaction of the chloride with water produced the hydrol.   The water furnishes a greater driving force than the alcohol, presumably by virtue of a greater tendency to solvate the chloride ion, but it is an ethoxyl ion derived from the alcohol which enters into combination with carbon.

FIG. VI-3.—Variation of rate with water content in the solvolysis of benzhydryl chloride.[17b]   ○ data of Norris and Morton; ● data of Ward; ◑ data of Farinacci and Hammett.

TABLE II.—THE COMPOSITION OF THE REACTION PRODUCT[17b]

[H₂O]	Rate constant ×10⁵	Mole percent benzhydrol	
		Found	Calculated
0.0	5.72	....	0
0.6004	7.90	1.8	27.7
1.320	10.57	11.8	46.0

In view of this evidence two otherwise possible mechanisms may be definitely excluded.   The reaction cannot be a four-body reaction of the type of the H_2—I_2 reaction (page 135) in which

[22] NORRIS and MORTON, J. Am. Chem. Soc., 50, 1795 (1928).

the hydrogen of the alcohol enters into combination with the halogen at the same time that the ethoxyl becomes combined with the carbon of the benzhydryl chloride. Nor can it be a direct displacement of chloride ion by an alcohol or water molecule

$$H-\overset{\underset{|}{H}}{O} \;' + \overset{C_6H_5}{\underset{C_6H_5}{\diagdown}}C\overset{H}{\underset{\bar{C}l\;'}{\diagup}} \rightarrow \left[H-\overset{\underset{|}{H}}{O} - \overset{\overset{C_6H_5}{|}}{\underset{C_6H_5}{C}} - H\right]^+ + [\;' \bar{C}l\;']^- \quad (VIII)$$
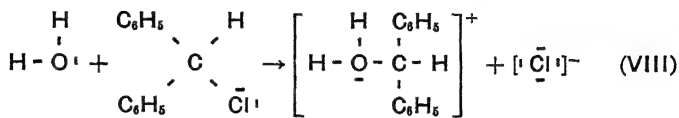
yielding the conjugate acid of benzhydrol. In either case the reaction of alkyl chloride with water must lead to hydrol not to its ethyl ether. Indeed the kinetics do not correspond to a second-order reaction of halide with water even when the halide reacts with small concentrations of water in an inert solvent. Table III cites the "second-order constants" $k = v/[RCl][H_2O]$ for the reaction of benzhydryl chloride with water in acetone. Far from being constant, these increase rapidly with increasing water concentration. This means that water is a specific

TABLE III.—HYDROLYSIS OF BENZHYDRYL CHLORIDE IN ACETONE[24]

H_2O	$10^7 k$
0.5556	6.39
1.1111	11.5
2.7778	47.5
5.5556	177.

catalyst for its own reaction with the chloride. More recent results[25] show that the alkyl chloride may also catalyze its own reaction. It seems probable, therefore, that the second-order reaction of benzhydryl chloride with water in alcohol solution is really a reaction of higher order involving the solvent alcohol as well. It is for this reason that these reactions have been called *polymolecular* solvolyses.[17]

The Structural Criterion for the Solvolytic Mechanism.— Further evidence against the nucleophilic displacement represented by equation (VIII) appears in the effect of changing structure of the alkyl group. Such displacements, regardless of the charge of the displacing group, have always been found to show a rate that decreases in the order methyl, ethyl, *i*-propyl,

[24] TAYLOR, *J. Chem. Soc.*, 1853 (1937); *J. Am. Chem. Soc.*, **60**, 2094 (1938).
[25] TAYLOR, *J. Chem. Soc.*, 478 (1939).

t-butyl (page 152). On the contrary, reactions involving an electrophilic attack on halogen or oxygen (items 10 to 13 of Table II, Chap. V) show a rate which, with the possible exception of methyl, increases in this order. It is the latter kind of structural effect that the solvolysis (item 14 of Table V, Chap. II) exhibits. Indeed the deviation of the methyl halide from the order set by the other halides may indicate that the displacement of equation (VIII) does occur to a significant extent with this alkyl, the one most favorable for it.

More exactly, the hydrolysis of an alkyl halide follows an equation of the type

$$v = k_1[\text{RCl}] + k_2[\text{RCl}][\text{OH}^-] \tag{10}$$

The first term on the right gives the rate of the solvolytic reaction, the second that of the direct displacement of halide ion by hydroxyl ion. In the case of all primary and some secondary alkyl halides, both k_1 and k_2 are measurable through determinations of the rate of reaction at various hydroxyl-ion concentrations. Because k_1 increases from primary to tertiary, while k_2 decreases, the second term becomes unmeasurably small with tertiary and with some secondary alkyl halides, even at large hydroxyl-ion concentrations. This is the case with α-phenylethyl chloride and *t*-butyl chloride the hydrolysis rates of which are not affected by the addition of alkali.

The Effect of the Solvolytic Reaction on Configuration.—With the exception of halogen acids and substances containing more than one center of asymmetry, the solvolytic reaction of an optically active halide leads to a product with the same sign of rotation as that obtained by the alternative path of the nucleophilic displacement. The two processes differ, however, in the magnitude of the rotation, racemization being negligible in the direct displacement, large in the solvolysis. Thus kinetic investigation has shown[26] that 88 per cent of the hydrolysis that β-*n*-octyl bromide undergoes in a N solution of sodium hydroxide in 60 per cent ethanol at 80° takes place by way of the second-order displacement of bromide ion by hydroxyl ion. Under these conditions the dextrorotatory bromide yields levo-

[26] HUGHES and SHAPIRO, *J. Chem. Soc.*, 1192 (1937). HUGHES, INGOLD, and MASTERMAN, *ibid.*, 1196 (1937).

rotatory alcohol with no more than 10 per cent racemization, and this probably due to the action of bromide ion on unreacted bromide. In acid solution the reaction goes entirely by the first-order solvolytic course. Dextrorotatory bromide still yields levorotatory alcohol, but it is racemized to the extent of 65 per cent. Similarly,[27] the conversion of α-phenylethyl chloride to the ethyl ether is 93 per cent second order in strongly basic ethanol solutions and is accompanied by no measurable racemization; in acid solution it is purely first order, the sign of the rotation is the same as that of the product from the alkaline solution, but racemization amounts to at least 70 per cent. The conversion of α-phenylethyl chloride to phenylethyl acetate[17a] in glacial acetic acid is first order, unaffected by the addition of sodium acetate. Chloride with a rotation of $+8.50$ yields acetate with one of -1.1. The reaction of the chloride with tetraethylammonium acetate (*i.e.*, acetate ion) in acetone is second order, hence a direct displacement. Chloride with a rotation of $+6.0$ yields acetate with the value -4.7.

The reaction of s-octyl bromide or of α-phenylethyl chloride with silver ion yields an alcohol of the same sign of rotation as that produced by the other reactions but less extensively racemized than in the solvolytic reaction.[28]

The Mechanism of the Solvolytic Reaction.—The hypothesis of a carbonium-ion intermediate in the solvolytic reaction[22,23,29a] is a reasonable and attractive one. If the rate-determining step is the formation of the ion, whereas the composition of the product depends upon its further reaction, such results as those of Table II are immediately accounted for. The hypothesis has some difficulties to meet, the most important being the fact that the product of the solvolysis is not completely racemized. The normal configuration of a carbonium ion is probably planar, hence symmetrical (page 66), and products formed from the ion would be expected to be racemic mixtures. If the ion retained the original configuration of the remaining groups

[27] HUGHES, INGOLD, and SCOTT, *J. Chem. Soc.*, 1201 (1937).

[28] HUGHES, INGOLD, and MASTERMAN, *J. Chem. Soc.*, 1236 (1937).

[29] (*a*) GLEAVE, HUGHES, and INGOLD, *J. Chem. Soc.*, 236 (1935). (*b*) OGG and POLANYI, *Trans. Faraday Soc.*, **31**, 604 (1935). HUGHES, *ibid.*, **34**, 209 (1938). INGOLD, *ibid.*, **34**, 222 (1938).

momentarily after the separation of the halide ion, retention rather than inversion of configuration in the product would be expected. The inversion can, however, be accounted for by supposing[29b] that the reaction of carbonium ion and solvent molecule occurs after the ionization has taken place but while the two ions are still so close together that the halide ion shields the carbonium ion against attack on the side from which the halide has separated. The racemized product is then attributed to those cases in which reaction occurs after the separation of the ions. This picture can be given greater precision by emphasizing the distinction between ionization and dissociation, between the solvation of the halide ion, with the accompanying electronic redistribution and probable shift in the relative positions of the nuclei, which converts the homopolar alkyl halide to an ion pair, and the subsequent separation of the ion pair.

This picture shades imperceptibly in theory and is experimentally indistinguishable from one in which the solvent molecule combines with the carbonium ion at the same time that the halogen lets go. Such a reaction would be termolecular or of higher order in principle, first order in practice because of the necessary constancy of the concentration of solvent molecules. It is convenient to refer to these reactions as involving a carbonium-ion intermediate, but this must not be interpreted to mean that it is a completely free intermediate or even that the recombination of the ion is not simultaneous with its formation. The essence of the distinction between the nucleophilic displacement and the solvolytic reaction, the basis of the profound difference in the way in which the two types of reaction respond to changes in structure (page 170), must be the difference in the nature of the attack on the alkyl halide and in the driving force involved. In the nucleophilic displacement the attack is on carbon, the driving force is the affinity of a nucleophilic reagent for carbon; in the solvolysis the attack is on halogen, the driving force is the affinity of solvent molecules for halide ion.

There is another difficulty. In the two cases in which a free carbonium ion is most clearly indicated by kinetic evidence, *viz.*, the addition of bromine to olefins (page 148) and the benzyl chloride-mercuric ion reaction (page 138), it reacts approximately as rapidly with nitrate, bromide, and chloride ions as

with water or methyl alcohol. In the free carbonium-ion mechanism of the solvolysis the reaction of carbonium ion with halide ion would reverse the first step

$$\text{RCl} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \text{R}^+ + \text{Cl}^- \tag{IX}$$

$$\text{R}^+ + \text{H}_2\text{O} \overset{k_2}{\rightarrow} \text{ROH} + \text{H}^+ \tag{X}$$
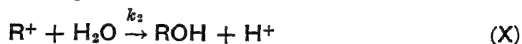
and the over-all specific rate k would become dependent upon the chloride-ion concentration in the form

$$k = \frac{k_1 k_2}{k_2 + k_{-1}[\text{Cl}^-]} \tag{11}$$

The fact that such a dependence is not observed argues against the free carbonium-ion mechanism.[17a]

Solvolytic reactions are not confined to alkyl halides. The hydrolysis of ethyl benzene sulfonate and various of its nuclear derivatives in 30 per cent ethanol exhibits a rate that, except in strongly alkaline solution, is independent of the concentration of hydroxyl ion.[30]

First-order Racemizations.—Certain racemizations take place by a process that closely resembles the solvolytic reaction. Thus α-phenylethyl chloride racemizes rapidly[31] in sulfur dioxide, a solvent that favors the ionization of halides. The rate is unaffected by the addition of chloride ion (tetraethylammonium chloride); hence the process is neither an inverting displacement of chloride ion by chloride ion, nor a reversible ionization followed by a rate-determining racemization of the ion. In the first case, chloride ion should accelerate the racemization, in the second it should retard by decreasing the extent of the ionization. The most probable alternative, a rate-determining ionization, is confirmed by the demonstration[32] that the rate of introduction of radioactive iodide ion into *t*-butyl iodide in sulfur dioxide is independent of the concentration of iodide ion, again indicating a rate-determining and measurably slow ionization.

[30] DEMÉNY, *Rev. trav. chim.*, **50**, 60 (1931).

[31] BERGMANN and POLANYI, *Naturwissenschaften*, **21**, 378 (1933). SZABO, Dis., Berlin, 1933.

[32] TUCK, *Trans. Faraday Soc.*, **34**, 222 (1938).

A variety of metal chlorides ($HgCl_2$, $ZnCl_2$, $SnCl_4$, BCl_3, $TiCl_4$, $SbCl_5$), the affinity of which for halide ion is demonstrated by the complex chloride ions that they form, racemize α-phenylethyl chloride.[21] Lithium chloride, *i.e.*, chloride ion, produces relatively little racemization under the same conditions. The racemization does not depend upon the reversible formation of styrene

$$C_6H_5 \text{-} CH_2 \text{-} CH_2 \text{-} Cl \rightleftharpoons C_6H_5 \text{-} CH = CH_2 + HCl \qquad (XI)$$
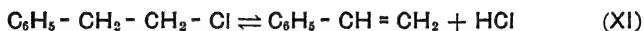
because the rate of addition of HCl to styrene under the conditions of the experiment is too small.[33] The rate of racemization depends markedly on the solvent as well as on the halide.

There can be no doubt that these racemizations depend upon an attack on the halide ion and involve intermediates of the same sort as those which occur in the solvolytic reaction. Like the solvolytic reactions, the racemization by complex-forming halides exhibits rates that vary as a higher power (1.3 to 14) of the concentration of the metallic halide and are, therefore, polymolecular.

The Effect of the Solvent.—An important light is thrown on the nature of the effect of differing solvents by recent experiments[34] on the solvolysis of t-butyl chloride. A very approximate estimate of the activity coefficient of the butyl chloride as a function of the solvent composition was obtained by the following method. The increase in total vapor pressure produced by the addition of butyl chloride to the solvent was measured and assumed to be equal to the partial pressure of the butyl chloride. Because the addition of the solute decreases the vapor pressure of the solvent, this assumption introduces an error of unpredictable magnitude into the resulting value of the activity coefficient. If, however, the error is neglected, the data on the solvolysis in alcohol-water mixtures are found to fit the equation

$$k = \frac{v}{N_B} = (k_w a_w + k_a a_a) f_B \qquad (12)$$

in which k is the first-order rate constant in terms of mole fractions, N_B is the mole fraction of butyl chloride, $f_B = a_B/N_B$, the

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[33] Böhme, *Ber.*, **71B**, 2372 (1938).

[34] Olson and Halford, *J. Am. Chem. Soc.*, **59**, 2644 (1937).

a's are activities, the k's are disposable parameters, and the subscripts w and a refer to water and alcohol, respectively. It is slightly more consistent with the equation[35]

$$k = (k_w N_w + k_a N_a) f_B \tag{13}$$

and with various equations involving squares or higher powers of concentration or activity of water and alcohol[35,36] such as

$$k = (k_{ww} N_w^2 + k_{wa} N_w N_a + k_{aa} N_a^2) f_B \tag{14}$$

Equations of the latter type are also consistent with the data[37] on the composition of the reaction product, which the linear forms are not.

The wide variety of applicable equations arises from the fact that the factor f_B has by all odds the most potent effect upon the variation of k, the variations of both being several hundred-fold. No conclusions about the mechanism with relation to the solvent molecules are, therefore, justified; in spite of the uncertainty in the values of f_B it seems, however, probable that the substitution of water for alcohol affects the reaction rate chiefly by increasing the activity of the halide. Those forces which favor the solution of the halide in alcohol as compared with water and decrease its activity in the former solvent are, therefore, unfavorable to its reaction.

In view of the Brønsted rate equation (page 127) these equations impose very definite limitations upon the possible variations of the activity coefficients of the transition states in the reactions with water and with alcohol.[35] This perhaps points the way toward the application of the Brønsted equation to gross changes in solvent composition as well as to salt effects.

The Case of the Halogen Acids.—The veil of confusion that long covered the Walden inversion phenomena in the reactions of halogen acids has now been lifted by kinetic investigations.[38] For instance, a solution of α-brompropionic acid in methanol is found to react by two kinetically distinguishable paths, one a

[35] BARTLETT, *J. Am. Chem. Soc.*, **61**, 1630 (1939).

[36] WINSTEIN, *J. Am. Chem. Soc.*, **61**, 1635 (1939).

[37] BATEMAN, HUGHES, and INGOLD, *J. Chem. Soc.*, 881 (1938); *J. Am. Chem. Soc.*, **60**, 3080 (1938).

[38] COWDREY, HUGHES, and INGOLD, *J. Chem. Soc.*, 1208 (1937).

first-order reaction of brompropionate ion or, less probably, a second-order one of brompropionic acid with methoxyl ion, the other a second-order reaction of brompropionate ion with methoxyl ion. The relative values of the rate constants are such that the second-order reaction strongly predominates in sodium methylate solutions of concentrations from 0.5 to 1M, and the first-order reaction in the region from 0.03 to 0.06M. In the presence of 1M base the ion of *d*-brompropionic acid yields *l*-methoxypropionic acid; in the presence of 0.077M base it yields the *d*-methoxy acid. This single experiment explains the classical difficulty that a "small" change in concentration of reagent or in other conditions of the reaction leads to a change in sign of rotation of the reaction product. The supposedly small change involves, in fact, a complete overturn in the reaction mechanism. .

In the methyl ester of the brompropionic acid both first- and second-order reactions are detectable but yield products of the same sign of rotation. These reactions are obviously the solvolysis and the nucleophilic displacement and must invert the configuration. Since the brom- and methoxy-esters may be obtained from the corresponding acids or converted to them by reactions that do not involve the asymmetric carbon, the knowledge thus obtained of the configurations of the two esters permits the proof that the second-order reaction of the ion inverts, but that the first-order reaction does not. Except for that due to side reactions, there appears to be no racemization in either of the reactions of the ion.

In aqueous solutions of brompropionic acid a second-order reaction with hydroxyl ion and a first-order reaction of brompropionate ion are observed. The lactic acid formed by the second-order reaction is inverted, that formed by the first-order reaction is not. In addition, there is a first-order reaction of brompropionic acid, which plays an important role in the reaction in sulfuric acid solutions and which inverts the configuration. The reaction of brompropionate ion with silver ion yields lactic acid with retention of configuration.[39]

The simplest interpretation[7,36] of these results is the hypothesis that the rate-determining step in the first-order reaction of

[39] COWDREY, HUGHES, and INGOLD, *J. Chem. Soc.*, 1243 (1938).

brompropionate ion or in the reaction with silver ion is the forma-
tion of an α-lactone, *e.g.*,

$$\left[\begin{array}{c} H \\ | \\ CH_3 - C\text{------}C = \bar{O} \text{ }| \\ | \qquad | \\ |Br| \text{ }|O| \end{array}\right]^- \rightarrow CH_3 - C \qquad + [\,|\bar{Br}\,|\,]^- \qquad (XII)$$
$$|O - C = O\,|$$
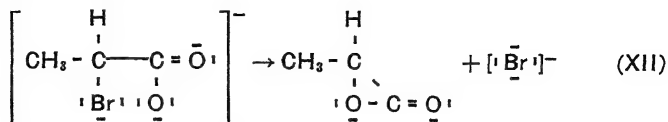
Whether this involves an internal nucleophilic displacement as
indicated or an attack by silver ion or solvent molecule on halo-
gen, the configuration of the α-carbon must be inverted. In
order that the configuration return to that of the original brom-
propionate ion, the subsequent hydrolysis of the lactone must
likewise invert.

The latter condition seemed a difficulty in view of the evidence
that the hydrolysis of esters has a mechanism that cannot allow
inversion of configuration (page 354). An α-lactone is, however,
an ester in which ring formation implies strain, and even in the
case of the relatively stable and isolable β-lactones hydrolysis
may have a mechanism that permits inversion.[40] The kinetic
study of β-butyrolactone reveals the presence of a reaction with
hydroxyl ion, of one catalyzed by oxonium ion, and of a third
reaction, the rate of which is independent of acidity and which
predominates in solutions in the neutral range. Every molecule
of *d*-lactone that reacts with hydroxyl ion or with oxonium ion
is converted to *l*-hydroxybutyric acid; every molecule that reacts
in the third reaction is converted to *d*-hydroxy acid. The prod-
uct is, therefore, predominantly levorotatory in strongly alkaline
or strongly acid solutions, predominantly dextrorotatory at
pH's from 1 to 9, and the magnitude of the rotation may be
quantitatively predicted from the pH of the solution and the rate
constants of the three reactions. There can be no doubt, there-
fore, that the hydrolysis of a lactone may invert, and it is probable
that it is the reaction in neutral solution that does so by way of a
sort of internal solvolytic reaction which ruptures the link
between oxygen and asymmetric carbon and allows a water
molecule to drop into the opposite side of the latter.

The impossibility of isolating α-lactones is not an argument
against their appearance as unstable intermediates. Indeed a

[40] OLSON and MILLER, *J. Am. Chem. Soc.*, **60**, 2687 (1938).

considerable body of evidence is accumulating for the formation of such three-ring systems. Aside from the addition of bromine to olefins (page 147), the following data are pertinent. The substance (A) undergoes a kinetically second-order reaction with

$$\begin{array}{ccc}
\underset{\underset{\underset{(A)}{\overset{\|}{\text{O}}\ \ \overset{|}{\text{Cl}}}}{}}{\text{C}_6\text{H}_5-\overset{\text{H}}{\underset{}{\text{C}}}-\overset{}{\underset{}{\text{C}}}-\text{C}_6\text{H}_5} &
\underset{\underset{(B)}{\text{OC}_2\text{H}_5\ \ \text{OH}}}{\text{C}_6\text{H}_5-\overset{\text{OC}_2\text{H}_5}{\underset{}{\text{C}}}-\overset{\text{H}}{\underset{}{\text{C}}}-\text{C}_6\text{H}_5} &
\underset{\underset{(C)}{\overset{\|}{\text{O}}\ \ \text{OH}}}{\text{C}_6\text{H}_5-\overset{\text{H}}{\underset{}{\text{C}}}-\overset{}{\underset{}{\text{C}}}-\text{C}_6\text{H}_5}
\end{array}$$
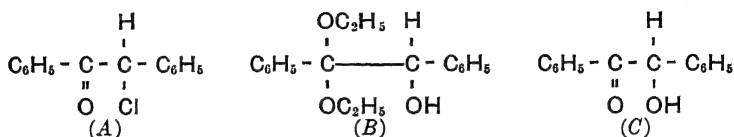
ethylate ion in ethanol solution and yields the hydroxyacetal (B) under conditions that do not lead to the conversion of the hydroxyketone (C) to the acetal.[41] The only reasonable inter-

$$\left[\begin{array}{c}
\overset{\cdot\overset{-}{\text{O}}\cdot}{\underset{\cdot\text{OC}_2\text{H}_5\ \cdot\overset{-}{\text{Cl}}\cdot}{\text{C}_6\text{H}_5-\text{C}}}
\text{----}
\overset{\text{H}}{\underset{}{\text{C}}}-\text{C}_6\text{H}_5
\end{array}\right]^{-}
\qquad
\begin{array}{c}
\overset{\overset{-}{\text{O}}}{\underset{\cdot\text{OC}_2\text{H}_5\ \ \text{H}}{\text{C}_6\text{H}_5-\text{C}}}
\text{----}
\text{C}-\text{C}_6\text{H}_5
\end{array}$$

$$\qquad\qquad (D) \qquad\qquad\qquad\qquad (E)$$
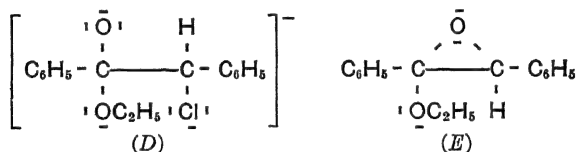
mediates are the ion (D) formed by a typical ketone reaction (page 329) and the oxide (E) formed by internal nucleophilic displacement from (D).

3-Brom-2-butanol is converted by HBr to dibrombutane with, very probably, retention of configuration.[42] This can be accounted for in terms of the addition of a proton to oxygen forming (F), an internal nucleophilic displacement with inversion leading to (G), and a displacement (with a second inversion) of the ring bromine by bromide ion leading to the dibrombutane (H)

$$\left[\begin{array}{c}
\text{H}\\
\text{CH}_3-\overset{}{\underset{}{\text{C}}}-\overset{-}{\text{Br}}\,\cdot\\
\text{H}-\overset{-}{\text{O}}-\overset{}{\underset{}{\text{C}}}-\text{CH}_3\\
\text{H}\ \ \text{H}\\
(F)
\end{array}\right]^{+}
\left[\begin{array}{c}
\text{CH}_3\\
\text{C}-\text{H}\\
\text{CH}_3-\text{C}-\overset{-}{\text{Br}}\,\cdot\\
\text{H}\\
(G)
\end{array}\right]^{+}
\begin{array}{c}
\text{H}\\
\text{CH}_3-\overset{-}{\underset{}{\text{C}}}-\overset{-}{\text{Br}}\,\cdot\\
\cdot\overset{-}{\text{Br}}-\overset{}{\underset{}{\text{C}}}-\text{CH}_3\\
\text{H}\\
(H)
\end{array}$$
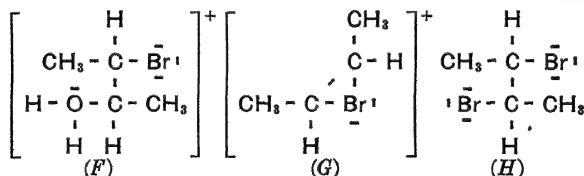
Molecules with Plural Asymmetry Centers.—If a halide of the structure (I) is converted into the carbonium ion (J) and then into the alcohol, two different substances having opposite con-

[41] Ward, *J. Chem. Soc.*, 1541 (1929).

[42] Winstein and Lucas, *J. Am. Chem. Soc.*, **61**, 1576 (1939).

figurations of the right-hand carbon may be formed.   Because of
the asymmetry of the other carbon these are different substances,
not merely enantiomorphic substances differing only in sign of
rotation.   Consequently, the rate constants for their formation
from (J) will be different, and they will not appear in equal
amounts.   The dissymmetry of the left-hand carbon induces a
dissymmetry of the electron system of the right-hand carbon,

$$
\begin{array}{ccc}
\begin{array}{c}
R_1 \ \ R_4 \\
| \ \ \ | \\
R_2 - C - C - Cl \\
| \ \ \ | \\
R_3 \ \ R_5 \\
(I)
\end{array}
&
\left[
\begin{array}{c}
R_1 \ \ R_4 \\
| \ \ \ | \\
R_2 - C - C \\
| \ \ \ | \\
R_3 \ \ R_5
\end{array}
\right]^+
&
\begin{array}{c}
R_1 \ \ R_4 \\
| \ \ \ | \\
R_2 - C - C - OH \\
| \ \ \ | \\
R_3 \ \ R_5 \\
(K)
\end{array}
\\
& (J) &
\end{array}
$$
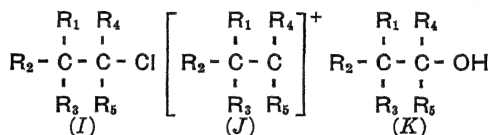
favors certain orientations of the groups attached to one carbon
with respect to those attached to the other, and hinders or aids
the access of oxygen in the one or the other configuration, *i.e.*,
leads to an asymmetric synthesis on the carbonium carbon.   If
the configuration of (I) is represented by the symbol dd, that of
the ion by d, and that of the two alcohols by dd and dl and if the
rate constants for the formation of the two alcohols from the ion
are k_{dd} and k_{dl}, then the initial composition of the reaction product
from a completely free carbonium ion would be

$$
\frac{[dl]}{[dd]} = \frac{k_{dl}}{k_{dd}} \tag{15}
$$

But it is known from the study of reactions in which only one
center of asymmetry is present that the carbonium ion is never
completely free; the reaction product contains both d and l
products, with the one formed by inversion of configuration
predominating.   Consequently, in the case of two centers the
composition of the reaction product must be given by the
inequality

$$
\frac{[dl]_{dd}}{[dd]_{dd}} > \frac{k_{dl}}{k_{dd}} \tag{16}
$$

instead of by equation (15).   If the original chloride has the
configuration dl, the carbonium ion is still d, but a predominance
of inversion in the reaction leads to

$$
\frac{[dl]_{dl}}{[dd]_{dl}} < \frac{k_{dl}}{k_{dd}} \tag{17}
$$

It is no longer possible to predict that the reaction product will contain a fraction greater than one-half of the product formed with inversion, but only that, *when two substances of dd and dl configurations react in the same way to form mixtures of isomeric products, the initial product produced from the dd reactant will contain a larger proportion of material of the dl configuration than will that from the dl reactant.*

Even in the limiting case, corresponding to complete racemization in the one center problem, in which the inequalities (16) and (17) reduce to equation (15), the composition of the product need not correspond to a preponderance of the more stable product. The relative stability is measured by the equilibrium constant K for the conversion of one alcohol into the other

$$K = \frac{[dl]}{[dd]} \text{ at equilibrium} \tag{18}$$

Like any other thermodynamic quantity it is independent of mechanism; hence it has the same value if the conversion of one alcohol to the other goes by way of the carbonium ion

$$dd \underset{k_{dd}}{\overset{k_{-dd}}{\rightleftharpoons}} \text{ion} \underset{k_{-dl}}{\overset{k_{dl}}{\rightleftharpoons}} dl \tag{XIII}$$

The constant K must equal the product of the equilibrium constants of the two steps of reaction (XIII), and by the usual relation between equilibrium and rate constants of a reversible reaction

$$K = \frac{k_{dl}k_{-dd}}{k_{dd}k_{-dl}} \tag{19}$$

The equilibrium mixture of the isomeric alcohols contains them, not in the ratio k_{dl}/k_{dd} of their rates of formation from the ion, but in a proportion that involves also the rates of the formation of the ion from the two alcohols.

No data are available for a verification of these conclusions on the hydrolysis of an alkyl halide, but an extensive investigation[43] of the conversion of amines to alcohols by the action of nitrous acid is pertinent because of the probability that this reaction

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[43] Hückel, *Ann.*, **533**, 1 (1938).

goes by way of a carbonium-ion intermediate (page 295).   The results are in fact consistent with the not very strenuous demands of the relations (16) and (17) and show, in some instances, a preponderance of an unstable isomer in the reaction product.

The Prediction of Configuration.—Enough cases have now been examined without contradiction to lend very considerable validity to the following principle. *Every displacement on an asymmetric carbon atom the rate of which is proportional to the concentration of the nucleophilic displacing ion or molecule involves an inversion of the configuration of the asymmetric atom.*   In terms of this principle the two problems of page 158 reduce to a single one in reaction kinetics: to recognize the relative configurations of reactants and products and to direct the course of reaction toward products of known configuration, one must learn the conditions that allow the kinetically second-order displacements the result of which alone is completely predictable.   A kinetically first-order reaction the rate of which is independent of the concentration of the group that enters into combination with the asymmetric carbon in the final product is a direct invitation to uncertainty, especially if plural asymmetry centers or the possibility of cyclic intermediates are present.   The fact that the hydrolysis of sugar toluenesulfonates is sometimes accompanied by inversion, sometimes by retention of configuration need, therefore, occasion no surprise.[44]   The hydrolysis of alkyl toluenesulfonates is likely to be first order (page 173), and both plural asymmetry centers and the possibility of cyclization are present.

Much remains to be done in the prediction of configurational changes accompanying common reactions.   Such familiar reactions as those which are used for the conversion of an alcohol to the corresponding chloride or bromide are, for instance, practically untouched from the point of view of kinetics and mechanism.   On the other hand, certain possibilities are clearly apparent.   One can expect to convert a dextrorotatory alcohol into its levorotatory isomer by the Kenyon and Phillips cycle of page 161 in high yield and with negligible racemization: there is every reason to hope that similar prescriptions for the preparation of products of known configuration in high optical purity will

[44] PEAT and WIGGINS, *J. Chem. Soc.*, 1088 (1938).

appear with further study in the light of principles that are now well established.

On Successive Displacements : A Catalytic Mechanism.—The toluenesulfonate of the levorotatory alcohol C_6H_5—CHOH—CH$_3$ reacts with ethyl alcohol in the presence of potassium carbonate to give the dextrorotatory ethyl ether $(\alpha = +4.50)$. The method of page 162 shows that the reaction is accompanied by inversion. But when the reaction is carried out in the presence of a large concentration of lithium chloride, the ethyl ether is formed with retention of configuration $(\alpha = -2.0)$.[10]   A similar result has been obtained with the carbinol C_6H_5—CHOH—CH_2—$CO_2C_2H_5$.[11]

A reasonable interpretation[10,11] of these results derives from the hypothesis that chloride ion reacts with the alkyl toluenesulfonate more rapidly than does alcohol and that this displacement and the subsequent alcoholysis of the alkyl chloride both invert. The two inversions lead to the original configuration. The correctness of this interpretation is a matter for kinetic investigation; its possibility is demonstrated by the behavior of the hydrolysis of methyl bromide in the presence of iodide ions.[45] The reactions

$$CH_3Br + I^- \rightarrow CH_3I + Br^- \qquad (XIV)$$

and

$$CH_3I + H_2O \rightarrow CH_3OH + I^- + H^+ \qquad (XV)$$
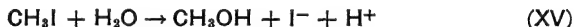
are so fast compared with

$$CH_3Br + H_2O \rightarrow CH_3OH + Br^- + H^+ \qquad (XVI)$$
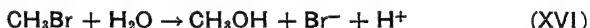
that a large proportion of the hydrolysis of the bromide may be diverted to the path of equations (XIV) and (XV) by small concentrations of iodide ion, and this makes iodide ion an active catalyst for the hydrolysis of the bromide.

Systems of this sort are models in terms of which the requirements for a homogeneous catalysis may be envisaged. Methyl bromide reacts more rapidly with iodide ion than with water, yet the complete solvolysis of the iodide proves that the former process is accompanied by a smaller decrease in free energy than the latter. This represents a glaring deviation from parallelism

[45] MOELWYN-HUGHES, *Proc. Roy. Soc.* (London), **A164,** 295 (1938); *J. Chem. Soc.,* 779 (1938).

between rate and equilibrium (page 136). Such a deviation is in fact necessary for a catalytic mechanism involving a carrier like the iodide ion of this case. It is, consequently, a problem of the first importance to discover the cause of these deviations, to learn why, for instance, methyl iodide, which may be produced by the displacement of bromide ion from methyl bromide, is more reactive than the latter toward reagents that displace iodide or bromide ions.

Another catalytic mechanism is suggested by the effect of water upon the reaction of benzhydryl chloride with alcohol (page 167). Here the effect of water is not the formation of definite intermediates, but rather the exertion of a profound influence upon the distribution between reactants and transition state.

It is upon the basis of one or the other of these processes that all the multitudinous catalytic phenomena of organic chemistry must be explained. These include acid and basic catalysis of condensation and hydrolytic reaction, the effect of alkali or of pyridine in the Schotten-Baumann reaction, and, most important, the startling and specific catalytic effects produced by enzymes. If enzyme chemistry is to advance beyond the stage of the empirical isolation of naturally occurring enzymes and the study of their behavior or of likewise empirical attempts to synthesize organic catalysts,[46] it must be by way of an understanding of these fundamental kinetic problems.

[46] LANGENBECK, "Die Organischen Katalysatoren und ihre Beziehungen zu den Fermenten," Berlin, 1935.

CHAPTER VII

THE EFFECT OF STRUCTURE ON REACTIVITY

Quantitative Relationships between Systems of Reactions.— It is one of the fundamental and most familiar assumptions of the science of organic chemistry that like substances react similarly and that similar changes in structure produce similar changes in reactivity. Yet the application of the principle requires so great an exercise of judgment, offers so wide an opportunity for the wisdom that comes only with experience and for the genius that seems almost intuition that there is some justice in the compliment or gibe, whichever it be, that this is an art not a science.

These complications arise, at least in part, from the presence of both kinetic- and potential-energy terms in the equations that determine equilibrium and rate of reaction (pages 77, 118). This is clearly shown by the simplification that results when attention is restricted to those cases in which rate and equilibrium are determined by potential energies alone, *viz.*, in the side-chain reactions of meta and para substituted benzene derivatives and in the reaction of substitution in the benzene ring. In these cases a simple and quantitative relationship appears when two *series* of rate or equilibrium constants are compared that differ with respect to the nature of the reacting group, the change which it undergoes during the reaction, or in the sense that the rate and the equilibrium constants of a single series of reactions are compared. The members of each series are identical in these respects but differ in the sense of a series of substitutions in the meta or para position relative to the reacting group. One series consists, for instance, of the ionization constants of meta and para substituted benzoic acids, another of the rate constants for the hydrolysis of similarly substituted benzoic esters. When, as in Fig. 1, the logarithms of the constants of one series are plotted against the logarithms of the constants of the other, the open

circles, which represent the meta and para derivatives of benzoic acid and benzoic ester, lie closely on a straight line. Each point in the figure is obtained by plotting as abscissa the logarithm of the ionization constant of benzoic acid or one of its derivatives and as ordinate the logarithm of the rate constant for the hydrolysis of the similarly substituted ethyl benzoate. For instance,

o m and p - benzoic derivs.
ⱺ o benzoic derivs.
ⱺ Aliphatic derivs.
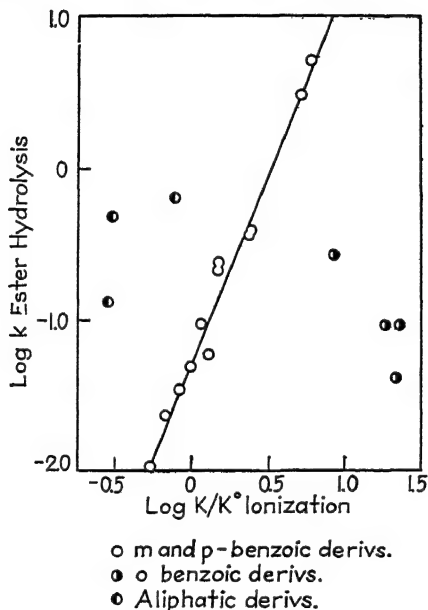
Fig. VII-1.—Comparison of hydrolysis rates of esters with ionization constants of acids.

the first open circle on the lower left is plotted from data on the ionization constant of p-methoxybenzoic acid and on the rate constant for the hydrolysis of ethyl p-methoxybenzoate. Each point is due to and represents in this way a particular substitution. The straight line, which has been drawn to produce the best fit to the points (according to the least-squares principle it is the one for which the sum of the squares of the deviations of the points from the line is a minimum), obeys an equation of the form

$$\log k_h = \rho \log K_i + A \tag{1}$$

in which k_h is the rate constant of the hydrolysis, K_i the ionization constant, ρ the slope, and A the intercept.

Reaction Constants and Substituent Constants.—Similar linear relationships of greater or less precision are found to apply to the rate and the equilibrium constants of practically all side-chain reactions of benzene derivatives.[1] It is almost obvious and easily demonstrated that two series of constants that are both linearly related in this way to a third are related in the same way to each other, the slope of the last relationship being the ratio of the slopes of the first two. Consequently, it is possible to relate the various series to one standard of reference, for which the ionization constants of substituted benzoic acids are especially suitable because of the many accurate values now available.[2] Equation (1) may be simplified by conversion to the form

$$\log k = \rho(\log K_i - \log K_i^\circ) + (A + \rho \log K_i^\circ) \qquad (2)$$

in which k is any rate or equilibrium constant and K° is the ionization constant of unsubstituted benzoic acid. The quantity $(A + \rho \log K_i^\circ)$ is necessarily equal to $\log k^\circ$ where k° is the rate or equilibrium constant for unsubstituted reactant; substitution of the definition

$$\sigma \equiv \log K_i - \log K_i^\circ \qquad (3)$$

converts equation (2) to the form

$$\log k - \log k^\circ = \rho\sigma \qquad (4)$$

The *substituent constant* σ is by definition determined by the nature of the substituent and independent of the reaction the constant k of which is involved in equation (4). The *reaction constant* ρ is by the nature of the linear relationship a constant for all substituents and depends only on the reaction series.

[1] (a) HAMMETT, *Chem. Rev.*, **17**, 125 (1935). (b) BURKHARDT, *Nature*, **136**, 684 (1935). (c BURKHARDT, FORD, and SINGLETON, *J. Chem. Soc.*, 17, (1936). (d) BURKHARDT, EVANS, and WARHURST, *ibid.*, 25 (1936). (e) HAMMETT, *J. Am. Chem. Soc.*, **59**, 96 (1937). (f) HAMMETT, *Trans. Faraday Soc.*, **34**, 156 (1938).

[2] (a) DIPPY and WILLIAMS, *J. Chem. Soc.*, 1888 (1934). (b) DIPPY, WILLIAMS, and LEWIS, *ibid.*, 343 (1935). (c) DIPPY and LEWIS, *ibid.*, 644 (1936). (d) BAKER, DIPPY, and PAGE, *ibid.*, 1774 (1937). (e) DIPPY and PAGE, *ibid.*, 357 (1938).

For all substituents for which an accurate value of the ionization constant of the correspondingly substituted benzoic acid is available, the value of σ is immediately given by the definition (3). For any reaction series for which data on a reasonable number of meta and para substituted derivatives are available, the value of the reaction constant ρ is obtained by plotting log k against σ, as is done in Fig. 2 for a number of reactions. The slope of the best straight line through the points, determined preferably by the method of least squares, is the value of ρ. If data for this reaction series are available for substituents for which σ is not known from ionization constants, these values may be obtained by substitution of the corresponding values of k in equation (4).

In this way it has been possible[1e] to set up a table of values of σ (Table I) and another of values of ρ (Table II). Table I contains in addition a notation (the number of the reaction series from Table II) of the source of the σ value, the number of reactions n for which data for each substituent are available, and the probable error or median deviation r of the value of σ for these reactions. Table II describes the reaction briefly and gives the values of ρ and of log k°, the number of substituents n for which data are available, and the probable error r. The last is the median deviation of the points from the best straight lines of the plots and is a measure of the probable precision of the prediction of
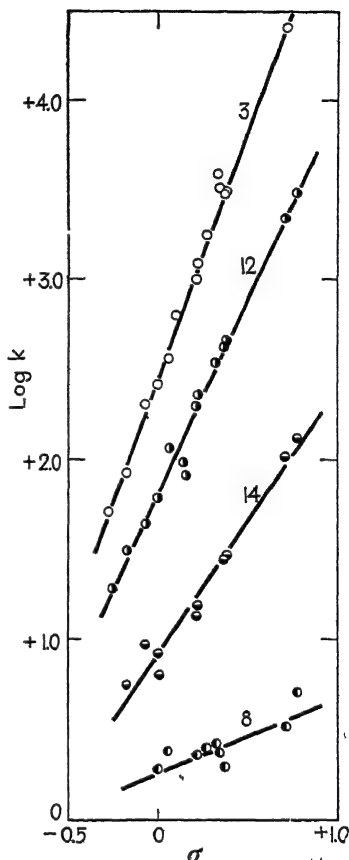
Fig. VII-2.—Relationship between log k and σ for various reactions (see Table II).[1e] The position of the scale of ordinates is arbitrary.

Table I.—Substituent Constants

Substituent	σ	Source	n	r
p-NH₂	−0.660	2	5	0.083
p-CH₃O	−0.268	1	47	0.063
p-C₂H₅O	−0.25	3	6	0.105
3,4-di-CH₃	−0.229	4	1	
m-(CH₃)₂N	−0.211	31	1	
p-(CH₃)₂N	−0.205	21[a]	1	
p-t-C₄H₉	−0.197	1	2	0.13
p-CH₃	−0.170	1	48	0.080
m-NH₂	−0.161	2	4	0.066
3,4-CH₂O₂	−0 159	2	3	0.017
p-C₂H₅	−0.151	1	2	0.03
p-i-C₃H₇	−0.151	1	2	0.09
m-CH₃	−0.069	1	32	0.045
p-CH₂CH₂CO₂H	−0.066	33	1	
p-CH₃S	−0.047	2	1	
m-CH₂CH₂CO₂H	−0.027	33	1	
None	0.000	1	55	0.043
p-C₆H₅	+0.009	2	3	0.22
p-F	+0.062	1	10	0.065
m-CH₃O	+0.115	1	9	0.102
m-CH=CH—CO₂H	+0.141	33	1	
m-C₂H₅O	+0.15	3	2	0.093
β-C₄H₄[b]	+0.17	3	9	0.102
m-C₆H₅	+0.218	33	1	
p-Cl	+0.227	1	40	0.054
p-Br	+0.232	1	30	0.043
p-I	+0.276	2	15	0.067
m-CH₃CO	+0.306	33	1	
m-F	+0.337	1	9	0.085
m-I	+0.352	1	12	0.056
m-CO₂H	+0.355	33	2	0.009
m-Cl	+0.373	1	26	0.053
m-CHO	+0.381	33	1	
m-Br	+0.391	1	21	0.051
p-CH=CH—CO₂H	+0.619[e]	33	1	
m-C₆H₅—N=N	+0.640	30, 31	1	
m-CN	+0.678	30, 31	1	
m-NO₂	+0.710	1	34	0.071
p-CO₂H	+0.728[e]	33	2	0.038
p-NO₂[c]	+0.778[e]	1	29	0.077
p-CH₃CO	+0.874[e]	33	1	
p-CN	+1.000[e]	4	4	0.042
p-CHO	+1.126[e]	33	1	
p-NO₂[d]	+1.27[d]	3	8	0.052

[a] A statistical factor of 2 was used in calculating the value of σ.

[b] β-Naphthalene derivatives.

[c] To be used for the reactions of all benzene derivatives except those of aniline and phenol.

[d] To be used for the reactions of derivatives of aniline and phenol.

[e] Tested only on phenol derivatives, probably valid only for these and for aniline derivatives.

TABLE II.—REACTION CONSTANTS
(E = equilibrium, R = rate)

Reaction	log $k°$	ρ	r	n
1. E. Ionization of benzoic acids, water, 25°[2]..	−4.203	+1.000	.....	14
2. R. Alkaline hydrolysis of ethyl benzoates, 87.83% ethanol, 30°[3]...................	−3.072	+2.498	0.067	12
3. E. Acidity constants of anilinium ions, water, 25°[4]............................	−4.569	+2.730	0.060	14
4. E. Ionization of phenols, water, 25°[5]......	−9.941	+2.008	0.047	5
5. R. Alkaline hydrolysis of ethyl cinnamates, 87.83% ethanol, 30°[3b,d]................	−2.700	+1.329	0.031	15
6. R. Esterification (N HCl) of benzoic acids, ethanol, 25°[6].........................	−3.755	−0.467	0.038	9
7. R. Bromination of acetophenones, $HC_2H_3O_2$-H_2O-HCl, 25°[7]...................	−4.375	−0.550	0.045	14
8. R. Same, $HC_2H_3O_2$-H_2O-$NaC_2H_3O_2$, 25°[8]..	−5.524	+0.417	0.060	10
9. E. Ionization of 5-subst.-2-furoic acids, water, 25°[9] (5 = p)....................	−3.180	+1.394	0.054	6
10. R. Alkaline hydrolysis of benzamides, water, 100°[10]..........................	−2.787	+1.055	0.035	13
11. R. Acid hydrolysis of benzamides, water, 100°[10]...............................	−3.513	+0.118	0.040	12
12. E. Ionization of phenylboric acids, 25% ethanol, 25°[11].......................	−9.699	+2.143	0.065	14
13. R. Solvolysis of benzoyl chlorides, ethanol, 0°[12]..................................	−4.071	+1.529	0.104	13
14. R. Same, methanol[13]....................	−3.363	+1.471	0.065	10
15. R. Benzoyl chlorides plus aniline, benzene, 25°[14]................................	−1.201	+1.217	0.035	4
16. R. Anilines with dinitrochlornaphthalene, ethanol, 25°[15].........................	−1.641	−3.690	0.085	6
17. R. Anilines with dinitrochlorbenzene, ethanol, 25°[16].........................	−3.899	−3.190	0.073	10
18. R. Same as 17, but at 100°[15].............	−2.382	−2.581	0.160	10
19. R. Dimethylanilines with CH_3I, acetone-water, 35°[17]..........................	−3.336	−2.743	0.041	6
20. R. Phenyldiethylphosphines with C_2H_5I, acetone, 35°[17]........................	−3.286	−1.088	0.040	5
21. R. Dimethylanilines with trinitrophenol methyl ether, acetone, 35°[18]..............	−4.500	−2.382	0.057	6
22. R. Dimethylanilines with trinitrocresol methyl ether, acetone, 25°[19]..............	−5.328	−2.903	0.038	4
23. R. Anilines with benzoyl chloride, benzene, 25°[14]................................	−1.152	−2.694	0.154	5

TABLE II.—REACTION CONSTANTS.—(*Continued*)

Reaction	$\log k^\circ$	ρ	r	n
24. E. Anilines with formic acid to formanilides, pyridine–water, 100°[20].............	+0.665	−1.453	0.036	11
25. R. Rate of reaction 24[21].................	−4.123	−1.219	0.034	9
26. R. Hydrolysis of formanilides, pyridine–water, 100°[21].......................	−4.724	+0.316	0.055	9
27. R. Hydrolysis of benzenesulfonic ethyl esters, 30% ethanol, 25°[22]...............	−5.262	+1.190	0.030	4
28. R. Hydrolysis of benzoyl chlorides, acetone–water, 0°[23]...........................	−3.269	+0.796	0.220	9
29. R. Benzenesulfonyl chlorides with benzene, Friedel–Crafts, 30°[24]...................	−4.314	−1.799	0.080	6
30. R. Phenolate ions with ethylene oxide, 98% ethanol, 70.4°[25]......................	−4.254	−0.946	0.043	9
31. R. Phenolate ions with propylene oxide, 98% ethanol, 70.4°[25]....................	−4.698	−0.771	0.046	9
32. R. Phenolate ions with ethyl iodide, ethanol 42.5°[25]........................	−3.955	−0.991	0.016	5
33. R. Acid hydrolysis of arylsulfuric acids, water, 78.6°[1c,27].......................	−2.522	−0.467	0.038	10
34. R. Benzonitriles with H_2S in alkaline alcoholic solution, 60.6°[3a].................	−3.699	+2.142	0.054	7
35. R. Alkaline hydrolysis of ethyl phenylacetates, 87.83% ethanol, 30°[3b]..........	−1.813	+0.824	0.071	6
36. E. Ionization of phenylacetic acids, water, 25°[2,28]................................	−4.288	+0.471	0.026	10
37. R. Hydrolysis of benzyl chlorides, acetone–water, 69.8°[29]........................	−4.529	−1.875	0.154	12
38. R. Benzyl chlorides with iodide ion, acetone, 20°[29]...........................	−3.723	+0.785	0.078	11
39. R. Ald-chlorimines with hydroxyl ion, 92.5% ethanol, 0°[30].....................	−1.796	+2.240	0.079	9
40. R. Alcoholysis of benzoyl chlorides, ether–alcohol, 25°[31]...........................	−4.997	+1.922	0.047	8
41. E. Ionization of phenylarsinic acids, water, 18°[32]..................................	−3.689	+0.823	0.086	4
42. E. Acidity constants of dimethyl-anilinium ions, 50% ethanol, 20°[33]................	−4.05	+3.99	0.12	12
43. E. Ionization of phenylpropionic acids, water, 25°[2e]...........................	−4.655	+0.212	0.011	8
44. E. Ionization of cinnamic acids, water, 25°[2e]	−4.447	+0.466	0.027	9
45. R. Decomposition in aqueous ammonia of C_6H_5—CO—NH—O—CO—C_6H_4X, 30°[34].	−4.634	+0.865	0.002	4

Table II.—Reaction Constants.—(*Continued*)

Reaction	log $k°$	ρ	r	n
46. R. Decomposition in aqueous ammonia of XC_6H_4CO—NH—O—CO—C_6H_5, 30°[34]....	−4.589	−2.597	0.059	5
47. R. Acid hydrolysis of ethyl benzoates, ethanol-water, 100°[35].................	−5.724	+0.031	0.007	7
48. R. Alkaline hydrolysis of benzyl acetates, 56% acetone, 25°[36].....................	−1.157	+0.760	0.021	5
49. R. Alkaline hydrolysis of ethyl phenylacetates, 56% acetone, 25°[36]................	−0.179	+0.907	0.150	6
50. R. Alkaline hydrolysis of ethyl benzoates, 56% acetone, 25°[36].....................	−2.513	+2.373	0.051	7
51. R. Acid hydrolysis of benzyl acetates, 56% acetone, 25°[36].........................	−4.527	−0.053	0.016	5
52. R. Acid hydrolysis of ethyl phenylacetates, 56% acetone, 25°[36].....................	−4.567	−0.134	0.026	6

[3] Kindler, (*a*) *Ann.*, **450**, 1 (1926); (*b*) *ibid.*, **452**, 90 (1927); (*c*) *ibid.*, **464**, 278 (1928); (*d*) *Ber.*, **69B**, 2792 (1936).

[4] Hall and Sprinkle, *J. Am. Chem. Soc.*, **54**, 3469 (1932). Hall, *ibid.*, **52**, 5115 (1930). Hammett and Paul, *ibid.*, **56**, 827 (1934). Farmer and Warth, *J. Chem. Soc.*, **85**, 1713 (1904).

[5] Hantzsch and Farmer, *Ber.*, **32**, 3080 (1899). Boyd, *J. Chem. Soc.*, **107**, 1538 (1915).

[6] Hartman and Borders, *J. Am. Chem. Soc.*, **59**, 2107 (1937).

[7] Nathan and Watson, *J. Chem. Soc.*, 217 (1933). Evans, Morgan and Watson, *ibid.*, 1167 (1935).

[8] Morgan and Watson, *J. Chem. Soc.*, 1173 (1935).

[9] Catlin, C. A., **30**, 935 (1936).

[10] Reid, *Am. Chem. J.*, **21**, 284 (1899); *ibid.*, **24**, 397 (1900).

[11] Branch, Yabroff, and Bettman, *J. Am. Chem. Soc.*, **56**, 937; 1850; 1865 (1934).

[12] Norris, Fasce, and Staud, *J. Am. Chem. Soc.*, **57**, 1415 (1935).

[13] Norris and Young, *J. Am. Chem. Soc.*, **57**, 1420 (1935).

[14] Williams and Hinshelwood, *J. Chem. Soc.*, 1079 (1934).

[15] Van Opstall, *Rec. trav. chim.*, **52**, 901 (1933).

[16] Singh and Peacock, *J. Phys. Chem.*, **40**, 669 (1936).

[17] Davies and Lewis, *J. Chem. Soc.*, 1599 (1934).

[18] Hertel and Dressel, *Z. physik. Chem.*, **B29**, 178 (1935).

[19] Hertel and Dressel, *Z. physik. Chem.*, **B23**, 281 (1933).

[20] Davis, *Z. physik. Chem.*, **78**, 353 (1911).

[21] Davis and Rixon, *J. Chem. Soc.*, **107**, 728 (1915).

[2'] Demény, *Rec. trav. chim.*, **50**, 60 (1931).

rate or equilibrium constant that may be made from the values of σ and that of ρ for the reaction in question.   Wherever possible, the original data have been recalculated in terms of the second as the unit of time, and the exceptions are indicated.

The verification of the linear relationship is satisfactory. Out of 52 reaction series, all that could be found where the effect of at least four substituents is known, there are 7 only for which the probable error is greater than 0.1, and 1 only for which it is greater than 0.2.   The mean value of the probable error for the whole table is only 0.060.   The meaning of this precision is visualized by Fig. 2, because the reactions the log k values of which are plotted have probable errors of about this magnitude.

Some of the deviations from the linear relationship result no doubt from experimental error in the actual measurement, in the purification of the materials, or in the failure to isolate a single reaction.   Others unquestionably represent the superposition of some smaller and entirely independent effect upon the influence that leads to the linear relation.   In either case the deviations are random ones, and there is no indication that a curved line would fit the data better than the straight one. The second-order effect that leads to the deviations may very well result from the kinetic-energy terms; for entropies of reaction and of activation in a series of reactions of this sort deviate from constancy by comparable amounts (page 121).

[23] BERGER and OLIVIER, *Rec. trav. chim.*, **46**, 516 (1927).

[24] OLIVIER, *Rec. trav. chim.*, **33**, 244 (1914).

[25] BOYD and MARLE, *J. Chem. Soc.*, **105**, 2117 (1914).

[26] GOLDSWORTHY, *J. Chem. Soc.*, 1254 (1926).

[27] BURKHARDT, HORREX, and JENKINS, *J. Chem. Soc.*, 1654 (1936).

[28] DIPPY and WILLIAMS, *J. Chem. Soc.*, 161 (1934).

[29] BENNETT and JONES, *J. Chem. Soc.*, 1815 (1935).

[30] HAUSER, LEMAISTRE, and RAINSFORD, *J. Am. Chem. Soc.*, **57**, 1056 (1935).

[31] BRANCH and NIXON, *J. Am. Chem. Soc.*, **58**, 2499 (1936).

[32] BREYER, *Ber.*, **71B**, 163 (1938).

[33] DAVIES and ADDIS, *J. Chem. Soc.*, 1622 (1937).   DAVIES, *ibid.*, 1865 (1938).

[34] RENFROW and HAUSER, *J. Am. Chem. Soc.*, **59**, 2308 (1937).

[35] TIMM and HINSHELWOOD, *J. Chem. Soc.*, 862 (1938).

[36] TOMMILA and HINSHELWOOD, *J. Chem. Soc.*, 1801 (1938).

In one case only, that of the p-nitro substituent, it is impossible to represent all reactions with one value of σ. Even here, however, it is not a question of a range of values but of two widely different ones. One of these, listed as $p\text{-NO}_2{}^d$ in Table I, yields satisfactory agreement with the reactions of aniline or phenol derivatives, the other, listed as $p\text{-NO}_2{}^c$, applies to the reactions of all other compounds. This effect may be more general; for the values for other meta directing substituents (COOH, CHO, CN, etc.) have been tested only on the reactions of phenols and amines. Doubt of their applicability to other benzene derivatives is emphasized by the available data in the case of the COOH group. In 50 per cent ethanol, log K for benzoic acid is -5.29; for m-phthalic acid, -4.45; for terephthalic acid, -4.38.[37] If the σ values obtained from phenol derivatives and listed in Table I applied, log K for terephthalic acid would be -3.55.

The data of Tables I and II compress into a small compass a large amount of experimental data and provide the material for the prediction of a wide variety of unknown rate and equilibrium constants. From them the effect of any substituent the σ value of which is known upon any reaction with known values of ρ and log k° may be estimated with a probable error of 0.06 in the logarithm or of 15 per cent in the value of the constant. Since the total variation in constant between p-amino and p-nitro derivatives may be as much as ten million fold, this is not unsatisfactory.

Theoretical Corollaries.—It is not, in principle, obvious that any quantitative relationship should hold between the effects of substituents on different reaction series. The process of substitution is an essentially discontinuous one; it is impossible to proceed from benzoic to nitrobenzoic acid by a gradual transition, yet it is possible to use a continuous mathematical function to correlate the effect of the discontinuous substitution upon the ionization of benzoic acid with its effect upon other reactions. This indicates strongly that all these effects of substitution depend upon some continuously variable structural parameter, to which the substitution of the nitro group for hydrogen assigns a particular value.[38]

[37] Kuhn and Wassermann, *Helv. Chim. Acta*, **11**, 44 (1928).
[38] Evans and Polanyi, *Trans. Faraday Soc.*, **32**, 1333 (1936).

Given the existence of a quantitative correlation, the fact that it is linear in the logarithms can be no mere accident; for the linear relationship between the logarithms of the constants is equivalent to a relationship between the quantities $-RT \ln k$, which are the free energies of reaction or of activation. The fact that the relationship applies to the free energy of activation in the rate problem in just the same way that it does to the thermodynamic free energy of reaction in the equilibrium case is strong evidence for the transition-state theory of reaction rates. The essence of that theory is, in fact, the idea that rate constants and equilibrium constants are cast of much the same material.

The limitations of the linear free-energy relationship are quite as significant as its successes. It does not apply to the effect of ortho substituents in benzene derivatives, it does not apply to the reactions of aliphatic compounds. This is shown in Fig. 1, in which the half-shaded circles, which represent the effect of these structural changes upon ionization constant and hydrolysis rate, deviate widely from the linear relationship established by the meta and para derivatives. The differentiation between meta and para substitution and all other structural changes appears also in the study of the effect of structure upon entropy of reaction (page 84) and of activation (page 123) and indicates strongly that the linear relation is fundamentally one between the potential-energy terms of the rate and equilibrium equations

$$\Delta E_{P1} = \rho \Delta E_{P2} + \text{constant} \qquad (5)$$

So long as the kinetic-energy terms are negligible, equation (5) requires a linear relationship between the free energies; when the kinetic-energy terms are important, the latter relationship fails.

The Electronic Theory of the Effect of Substituent.—Just as equation (4) reduces the practical problem of predicting the effect of a substituent upon rate or equilibrium to the determination of the values of σ and ρ, so it reduces the theoretical problem of accounting for the effects of substituents to that of explaining the magnitudes of the same quantities. This may be satisfactorily done in terms of an "electronic theory,"[39] which discusses

[39] (a) LAPWORTH, *Nature*, **115**, 625 (1925). (b) ALLAN, OXFORD, ROBINSON, and SMITH, *J. Chem. Soc.*, 401 (1926). (c) INGOLD and INGOLD, *ibid.*, 1310 (1926). (d) INGOLD, Annual Reports of the Chemical Society, **129** (1926); (e) *Rec. trav. chim.*, **48**, 797 (1929); (f) *Chem. Rev.*, **15**, 225 (1934).

the phenomena in terms of internal electronic displacements and visualizes two ways in which the substitution of another group for ring hydrogen may alter the electronic density on the other atoms of the benzene ring. One called the *inductive effect*[39c,d,e,f] depends upon electrostatic effects. The simplest example is the NH_3^+ group in anilinium ion, the positive charge of which must exert a pronounced pull on all the electrons of the molecule; such a group is an electron sink, whereas the COO^- group in benzoate ion is for the same reason an electron source. But a group carrying no net charge may be source or sink by virtue of its charge distribution. Thus the removal of the valence electrons from a chlorine substituent would leave a *kernel* with a positive charge of 7, the kernel of the hydrogen that the chlorine replaces has a charge of only $+1$. Consequently, the substitution introduces a region of comparatively high positive-charge density in the immediate neighborhood of the ring. Even though this is balanced by the more distantly removed valence electrons of the chlorine, it exerts an attraction on the electronic system of the molecule.

The other effect, called the *tautomeric*, can best be visualized in terms of the resonance concept. Chlorbenzene may be pictured as a resonance hybrid (A). Because of the presence in it

(*A*)
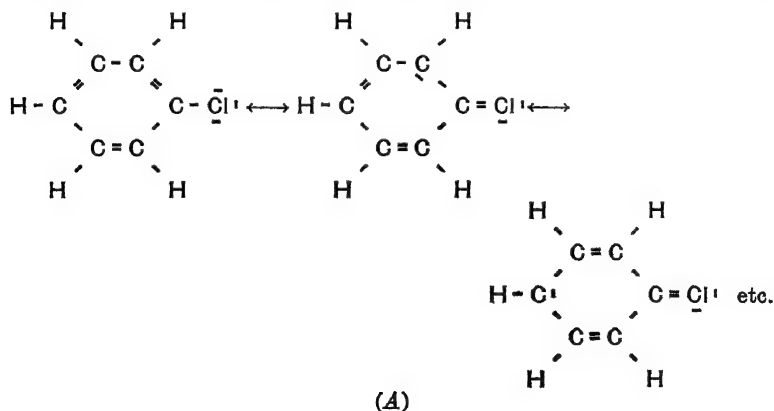
of structures in which electrons from the chlorine have been transferred to the ortho and para carbons, the electron density on these is higher than would be predicted from the classi-

cal formula.   In nitrobenzene, on the other hand, the resonance

$$
\begin{array}{ccc}
\underset{\text{H}}{\overset{\text{H}\quad\text{H}}{\text{C}-\text{C}}} \quad \bar{\text{O}}\, & & \underset{\text{H}}{\overset{\text{H}\quad\text{H}}{\text{C}-\text{C}}} \quad \bar{\text{O}}\, \\
\text{H}-\text{C}\qquad\quad \text{C}-\text{N} \quad \longleftrightarrow \quad \text{H}-\text{C}\qquad\quad \text{C}=\text{N} \quad \text{etc.} \\
\underset{\text{H}}{\overset{\text{C}=\text{C}}{\text{H}}} \quad \underset{\text{O}}{\bar{\text{O}}}\, & & \underset{\text{H}}{\overset{\text{C}=\text{C}}{\text{H}}} \quad \underset{\text{O}}{\bar{\text{O}}}\,
\end{array}
$$

(B)
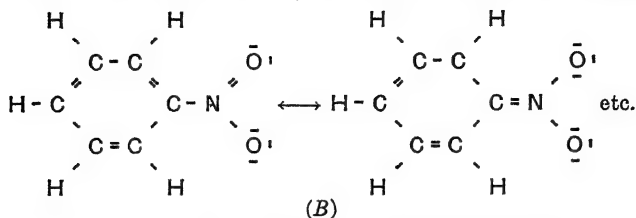
withdraws electrons from the ortho and para carbon atoms.

The result of the two effects must be a decrease in electron density in those cases in which σ is positive, an increase when it is negative.   Thus the positive value of σ for the NO_2 group means that this group decreases the work required to remove a proton from benzoic acid (it increases the ionization constant); since this involves the separation of the proton from its bonding electrons, a decrease in electron density must facilitate it.

In terms of this theory the quantity $-\sigma$ measures a change in electron density produced by a substituent, the quantity ρ measures the susceptibility of the reaction in question to changes in electron density.

The Interpretation of the σ Values.—A substituent produces, in general, different changes in electron density on the different carbon atoms of the ring; consequently, its effect differs according to the relative positions of substituent and reacting group.   The tautomeric effect, in principle, affects directly only the ortho and para positions, and its indirect effect on the meta positions must be smaller than the direct one.   In practice, the same thing appears to be true of the inductive effect, since the methyl group, for which no tautomeric effect is possible, exerts a greater effect in the para position ($\sigma = -0.170$) than it does in the meta position ($\sigma = -0.069$) relative to the reacting group.   The nitro group for which both the inductive effect due to the charge of the nitrogen kernel and the tautomeric effect (B) tend to decrease electron density likewise shows a greater effect in the para ($+0.778$ or $+1.27$) than in the meta ($+0.710$) position.   With the halogens and the methoxyl group the two effects are opposed, the inductive effect tending to decrease the electron density on all the ring atoms, the tautomeric effect to increase it specifically in the ortho and para positions.   In the case of the halogens the

result is a decrease in density all over the ring but a smaller decrease in the para than in the meta position. Unlike the methyl and nitro groups, these substituents exert an effect of greater magnitude in the meta ($\sigma = 0.337$ to 0.391) than in the para ($\sigma = 0.062$ to 0.276) position. In the case of the methoxyl group the conflict leads to opposite signs of σ in the meta and para positions, the values being -0.268 for para and $+0.115$ for meta.

The Interpretation of the ρ Values.—The sign of the value of ρ may be predicted when the substitutions are made in the A or the C component of the typical displacement reaction. This is the case in the ionization of benzoic acid (page 196), phenol, or aniline, where the B component is the proton. It is equally true in the reaction (19 of Table II) of dimethylanilines with methyl

$$\underset{\text{A}}{C_6H_5N(CH_3)_2} + \underset{\text{BC}}{CH_3I} \rightarrow \underset{\text{AB}}{C_6H_5N(CH_3)_3^+} + \underset{+\ \text{C}}{I^-} \qquad (1)$$
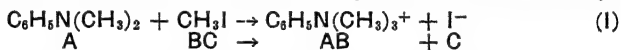
iodide in which a high electron density on the nitrogen favors the formation of a new bond to carbon which utilizes the unshared electrons of the nitrogen. The favorable effect of high electron density implies a negative value of ρ.

The problem is more difficult when the B component of the displacement reaction carries the substituents. If the displacement is nucleophilic, a decrease in electron density favors the formation of the new link, which tends to increase ρ, but it is unfavorable to the rupture of the old one, which tends to decrease ρ. The balance is difficult to predict[40] and may lean toward either side. Thus the reaction of pyridine with $C_6H_5CH_2Br$ shows a negative value of ρ, that of pyridine with C_6H_5CO—CH_2Br a positive one.[41]

A final obstacle in the path of a prediction of even the sign of ρ is the fact that many reactions are still of unknown mechanism. A prediction of the magnitude of the quantity is, of course, much more difficult. It is in some cases very sensitive to small changes in the nature of the reacting system. Thus the value is -0.946

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[40] Hinshelwood, Laidler, and Timm, *J. Chem. Soc.*, 848 (1938), discuss this problem in slightly different terminology. Since the linear free-energy relationship applies only in cases in which the effect of a substituent upon free energy of activation is the same as its effect upon heat of activation, it necessarily implies a linear relationship in the latter quantities.

[41] BAKER and NATHAN, *J. Chem. Soc.*, 519 (1935).

for the reaction (reaction 30 of Table II) of a series of phenolate ions with ethylene oxide, and -0.771 for the reaction of the same series of substances with propylene oxide (reaction 31).

Orientation in the Benzene Ring.—The electron-displacement theory also accounts most satisfactorily for orientation and reactivity in ring-substitution reactions, in fact it was largely derived from the study of this problem.[39]   This appears qualitatively in such familiar phenomena as the following: Substituents the σ value of which is negative in the para position and less negative or positive in the meta position (CH_3, CH_3O) increase the reactivity of the ring in nitration, halogenation, and similar reactions and yield chiefly ortho and para derivatives.   This indicates that these reactions are favored by high electron density.   Since this is higher in the para position of toluene or anisole than in the meta positions of the same substances or in benzene, reaction is faster in the para position than in the meta and faster than in benzene.   In agreement with the large positive value of σ for the nitro group, more positive in the para than in the meta position, nitrobenzene is less reactive than benzene, and substitution takes place mostly in the meta position.   The σ values for the halogens indicate that these decrease the electron density on all positions, but to a greater extent on meta.   In agreement with this, the halogen benzenes resemble nitrobenzene in being less reactive than benzene but orient ortho para like toluene.

The quantitative correspondence of theory and experiment appears in recent competitive measurements which short-circuit the problem of the unknown and complicated order and mechanism of the substitution reaction.[42]   By nitrating a mixture of benzene and toluene under standard conditions (acetyl nitrate in acetic anhydride) and determining the proportions of nitrobenzene and of the various nitrotoluenes in the reaction product, it is possible to determine the relative values of their specific rates of formation, subject only to the assumption that all the reactions are of the same order (page 124).   By application of suitable statistical factors (pages 124, 200) the relative reactivity

[42] INGOLD, LAPWORTH, ROTHSTEIN, and WARD, *J. Chem. Soc.*, 1959 (1931). BIRD and INGOLD, *ibid.*, 918 (1938).   INGOLD and SMITH, *ibid.*, 905 (1938). BEDFORD and INGOLD, *ibid.*, 929 (1938).

of a carbon atom in benzene and in the various positions in toluene may then be calculated. Similar experiments with halogen benzenes and with ethyl benzoate lead to values of the relative reactivity of the ring atoms in these compounds. The logarithms of these reactivities (log k) are plotted against σ in Fig. 3, the σ values for CO_2H being used instead of the unknown but probably identical values for $CO_2C_2H_5$. The parallel trend
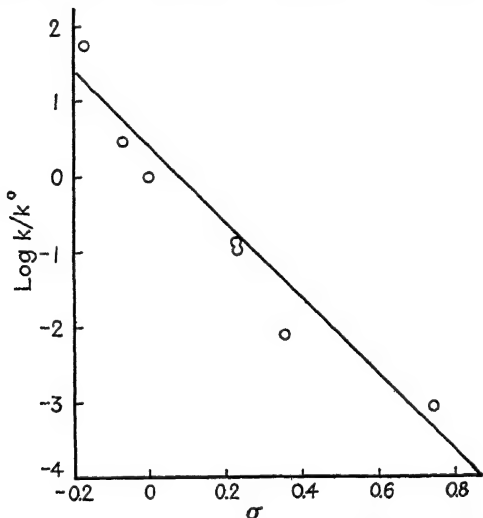
FIG. VII-3.—Comparison of relative reactivity in nuclear substitution reactions ($k/k°$) with the substituent constant σ.

of the values of log k and σ is obvious, and the value of ρ for nitration under the conditions used is of the order of five.

The Electrical-field Theory of Substituent Effects.—Another approach to the substituent problem was initiated[43] by the consideration of the relation between the first and second ionization constants of a symmetrical dibasic acid. If there were no influence of one acid group on the other, the first constant would be four times greater than the other for statistical reasons which may be derived from the following considerations. The equilibrium constant K_1 is the ratio of the specific rates k_1 and k_{-1} for the removal of a proton from $HOOC(CH_2)_xCOOH$ and for the addition of a proton to $HOOC(CH_2)_xCOO^-$. Similarly, the

[43] BJERRUM, *Z. physik. Chem.*, **106**, 219 (1923).

second ionization constant K_2 is the ratio of the specific rates k_2 and k_{-2} for the removal of a proton from the singly charged ion and for the addition of a proton to $^-OOC(CH_2)_xCOO^-$. But there is a factor of 2 in favor of k_1 over k_2 because there are two protons in the neutral acid and only one in the singly charged ion. There is a similar factor of 2 in favor of k_{-2} over k_{-1} because of the two positions in which the proton may add in the doubly charged ion. Hence in the absence of any interaction between the groups, $k_1 = 2k_2$, $k_{-2} = 2k_{-1}$, and

$$K_1 = \frac{k_1}{k_{-1}} = \frac{2k_2}{\frac{1}{2}k_{-2}} = 4K_2 \tag{6}$$

Statistical factors of the nature of the 4 in this equation have appeared in connection with benzene substitution (page 124) and are easily derived in many cases. Thus the first ionization constant of a dibasic acid should be twice as great as the ionization constant of its monoethyl ester if the structural influence of the ethyl group in $C_2H_5OOC(CH_2)_xCOOH$ is the same as that of the proton in $HOOC(CH_2)_xCOOH$.[44] The ratio is actually close to 2 in many but not all cases.[44,45]

The ratio of the first and second ionization constants of dibasic acids is, however, in all cases greater than the statistical factor of 4. This means that the group COO^- present in the ion makes the removal of the second proton more difficult than the first, for which the corresponding group is the electrically neutral COOH group. The extra free energy involved in the case of the ion is

$$\Delta G^\circ = -RT \ln K_1 + RT \ln 4K_2 \tag{7}$$

If this free energy is identified with a potential-energy quantity, the electrical work necessary to remove the second proton against the attraction exerted by the charge on the COO^- group, *viz.*,

$$\Delta E_P = -\frac{e^2}{\epsilon r} \tag{8}$$

the equation

$$RT \ln \frac{K_1}{4K_2} = \frac{e^2}{\epsilon r} \tag{9}$$

is obtained.[43]

[44] WEGSCHEIDER, *Monatsh.*, **16**, 153 (1895).
[45] GREENSPAN, *Chem. Rev.*, **12**, 339 (1933).

The available data on ionization constants lead by way of equation (9) to values of r, the distance between the two carboxyl groups, which are at least of the correct order of magnitude (Table III) and which increase with increasing length of the carbon chain between them. Further, the difference between maleic and fumaric acids is in the expected direction, and the ratio K_1/K_2 has a greater value in methanol in water, although the change is not so large as that predicted from the dielectric constants.[46] When, however, the data are more closely examined, a number of difficulties appear. (1) The value of r in the short-chain acids is much too small. (2) The average increase in r for each CH_2 group in straight chain acids is 1.73A, whereas the

TABLE III.—FIRST AND SECOND IONIZATION CONSTANTS OF DIBASIC ACIDS[47]

Acid	$10^5 K_1$	$10^6 K_2$	K_1/K_2	$r(A)$
Malonic	177.0	4.37	405.	1.5
Succinic	7.36	4.50	16.35	5.0
Glutaric	4.60	5.34	8.61	9.2
Adipic	3.90	5.29	7.37	11.5
Pimelic	3.33	4.87	6.84	13.2
Suberic	3.07	4.71	6.52	14.5
Azelaic	2.82	4.64	6.08	16.8
β-Methylglutaric	5.77	0.628	91.9	2.27
β,β-Dimethylglutaric	20.3	0.551	369.	1.57
β,β-Diethylglutaric	30.4	0.0785	3870.	1.02
Maleic	1200.	0.595	20,200.	1.19
Fumaric	95.7	41.3	23.17	5.25

value expected from the covalent radii and bond angles (page 31) is not more than 1.29A and is less if the chain is bent or coiled. (3) The extremely small values of r obtained with the alkyl-

H - O   CH₂   CH₂   O   CR₂   CR₂

C   CH₂   C   C   C

O   OH   O OH OH O

(C)   (D)
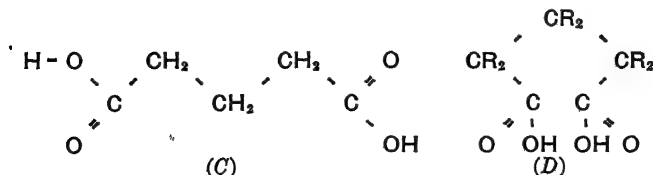
[46] EBERT, *Ber.*, **58B**, 175 (1925).

[47] GANE and INGOLD, *J. Chem. Soc.*, 1594 (1928). GERMAN, VOGEL, and JEFFERY, *Phil. Mag.*, **22**, 790 (1936).

substituted acids can be accounted for only by the purely *ad hoc* assumption that the alkyl groups convert the extended structure (*C*) of the unsubstituted acid to a coiled form (*D*).

The theoretical argument for equation (9) is weak in the following respects: (1) The kinetic-energy terms in the equilibrium equation have been disregarded. (2) Internal electron displacements in addition to the external field are not considered. (3) Electrical theory based on the hypothesis of a continuous dielectric medium meets difficulties when the distances involved are of the same order of magnitude as the dimensions of the molecules of the dielectric. (4) The dielectric constant of the acid molecule, which occupies part of the space between the charge and the ionizable proton, is smaller than that of the solvent medium.[48]

An attempt to correct for weakness 3[49] leads to values of r which avoid difficulties 1 and 2 but still yield low values for the

TABLE IV.—THE KIRKWOOD-WESTHEIMER TREATMENT OF DIBASIC ACIDS

Acid	r(obs.)	r(calc.)
Oxalic	3.85	3.50– 4.44
Dimethylmalonic	4.15	4.12– 4.87
Tetramethylsuccinic	4.80	4.66– 6.66
Succinic	5.85	4.66– 6.66
Glutaric	7.00	5.15– 7.39
Suberic	9.30	6.38–11.46

alkyl-substituted acids. On the other hand, a mathematical treatment that avoids weakness 4 by treating the acid molecule as a spherical or ellipsoidal cavity of low dielectric constant (2.0) in a solvent medium of high dielectric constant (80 for water) leads to reasonable values in all cases,[50] as the data of Table IV demonstrate. The calculated values in this table include as a maximum the value calculated on the basis that the acid molecule is stretched to the fullest extent permitted by the normal covalent radii and bond angles; as a minimum, an averaged value, the root mean square, calculated on the basis of

[48] SCHWARZENBACH, *Z. physik. Chem.*, **A176**, 133 (1936).

[49] INGOLD, *J. Chem. Soc.*, 2179 (1931).

[50] KIRKWOOD and WESTHEIMER, *J. Chem. Phys.*, **6**, 506; 513 (1938).

free rotation about all the bonds. The great improvement that results from this correction of the simple electrical-field theory arises from the fact that the electrical lines of force are constrained to pass to a greater extent through the molecule in the case of short-chain or alkyl-substituted acids. This is equivalent to a decrease in the effective dielectric constant and, consequently, to an incorrectly small value of r when the dielectric constant of the solvent is used in equation (9).

The quantity $K_1/4K_2$ measures the effect of a substitution, that of COO^- for $COOH$, upon the ionization constant, and the field theory attributes the effect solely to the charge on the former group. An electrically neutral substituent also produces an electrical field by virtue of its dipole moment. In terms of the same approximations as those of equation (9), the effect of a substituent should be given by[51]

$$\Delta G^\circ = -RT \ln \frac{K}{K^\circ} = \frac{e\Delta(\mu \cos \theta)}{\epsilon r^2} \qquad (10)$$

$\Delta(\mu \cos \theta)$ is the difference between the components in the direction of the ionizable proton of the dipole moments of the substituent group and of the C—H group that it replaces. Equation (10) leads, however, to values of the free-energy difference that are about ten times too small. The theory may be improved by the Kirkwood-Westheimer method and then yields correct values for ΔG° with reasonable values of r, but still fails to account for temperature and medium effects.

It seems indeed clear that any treatment of this sort is an approximation, an approach from another direction to phenomena that may also be approximated in terms of internal electron shifts complicated by an effect upon the internal charge distribution of the dipoles of the medium. The greatest weakness of the field theory in its present state is its inability to account for differences in the magnitude of the quantity ρ in different reactions. Thus the effect of a substituent upon the free energy of ionization of phenylboric acid is over twice as great ($\rho = 2.143$) as it is upon that of benzoic acid, even though the value of r and the molecular shape and dimensions must be

[51] WATERS, *Phil. Mag.*, **8**, 436 (1929). WOLF, *Z. physik. Chem.*, **B3**, 128 (1929).

nearly the same in the two cases. The same problem arises with anilinium ion ($\rho = 2.730$) and phenol ($\rho = 2.008$).[52] On the other hand, the linear free-energy relationships make it very difficult to suppose that there are two different effects of a substituent, following different laws.

In the hydrolysis of esters of dibasic acids the rate constants show a statistical factor of 2 in favor of the first step of the hydrolysis as against the second. In the acid hydrolysis the first step converts the group COOR into COOH, the effect of which upon the rest of the molecule should be nearly identical. Consequently, the ratio of the rate constants should be and is equal to the statistical factor, having the experimental value of 2.00 with the methyl and ethyl esters of succinic and tartaric acids.[53] The first step in the alkaline hydrolysis, however, converts the group COOR into the COO⁻ which by virtue of its charge has a pronounced effect upon the free energy of activation involved in bringing up a hydroxyl ion for the second step. The equation[54]

$$-RT \ln \frac{k_1}{2k_2} = \frac{e^2}{\epsilon r} \tag{11}$$

derived in the same way as equation (9), leads to closely similar values of r for related acids and esters.

The Proximity or Ortho Effect.—The effect of a substituent at a point in the molecule close to the reacting group may be different in kind from that which it exerts at a more distant point. The phenomenon was first recognized as "steric hindrance" in the acid-catalyzed esterification of benzoic acids,[55] in which the rate of reaction is appreciably reduced by a single methyl, halogen, or nitro group in the ortho position (Table V) and so powerfully by substitution in both ortho positions that conditions which otherwise lead to quantitative yields result in negligible

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[52] For other comparisons of the effect of substituents in different reactions in terms of the field theory, see Schwarzenbach, *Helv. Chim. Acta,* **15,** 1468 (1932); **16,** 522; 529 (1933); **17,** 1176; 1183 (1934); *Z. physik. Chem.,* A**176,** 133 (1936). Schwarzenbach and Epprecht, *Helv. Chim. Acta,* **19,** 493 (1936).

[53] Ingold, *J. Chem. Soc.,* 1375 (1930).

[54] Ingold, *J. Chem. Soc.,* 2170 (1931).

[55] Meyer, *Ber.,* **27,** 510 (1894).

reaction. The characteristic features of this as of all similar cases are the unexpectedly large effect of the double substitution, the fact that methyl and nitro groups produce effects in the same direction, and the relatively large magnitude of the effect of the ortho substitution. Substituents in meta and para positions have little effect upon the esterification rate ($\rho = -0.467$). A similar pronounced retardation by double ortho substitution, regardless of the nature of the substituents, is a characteristic feature of the reactions of carboxylic esters, amides, ·and acid halides, and of nitriles, ketones, and amines and is a well-recognized phenomenon in preparative chemistry.[56]

TABLE V.—EFFECT OF ORTHO SUBSTITUENTS ON EQUILIBRIA AND RATES
A few para substituents are included to set the scale of the effect. The data are the ratios $K/K°$ or $k/k°$ where $K°$ and $k°$ are equilibrium and rate constants for the unsubstituted compound. The reaction numbers are those of Table II

Substituent	1. Acid ionization constants[2,57]	2. Benzoic ester hydrolysis rates[3,58]	3. Acidity constants anilinium ions[4]	5. Cinnamic ester hydrolysis rates[3]	6. Esterification rates, benzoic acids[6]	18. Aniline reaction rates[15]	33. Aryl sulfuric acid- hydrolysis rates[26,27]
p-CH₃	0.676	0.467	0.33	0.711	0.560	2.47	0.771
p-Cl	1.67	4.32	3.8	2.03	0.610	0.277	1.21
p-NO₂	6.00	103 9	3,100.	9.78	.....	<0.001	5.00
o-CH₃O	1.286	....	1.2	0.376	.....	0.579	1.49
o-CH₃	1.96	0.124	1.6	.....	0.260	0.103	0.870
o-F	8.63	5.55	....	2.34			
o-Cl	18.2	1.910	65.	1.99	.....	<0.001	1.46
o-Br	22.3	1.887	96.	3.06	0.475		
o-I	21.9	0.835	....	2.52			
o-NO₂	107.0	5.71	58,000.	7.93	0.066	<0.001	4.02
o-C₆H₅	5.53	....	....	.....	.....	0.036	0.747
o-C₂H₅	....	....	1.3	.....	.....	....	0.357

The data listed in Table V show that reactions 1, 2, 3, 6, and 18 exhibit the characteristic phenomena that *o*-methyl and *o*-nitro groups have effects in the same direction and that ortho substituents have effects of a quite different magnitude from those in the meta and para positions. Since the effects are just

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[56] GOLDSCHMIDT, "Stereochemie," Leipzig, 1933, pp. 222*ff*.
[57] DIPPY and LEWIS, *J. Chem. Soc.*, 1426 (1937).
[58] EVANS, GORDON, and WATSON, *J. Chem. Soc.*, 1430 (1937).

as pronounced in the equilibria 1 and 3 as in the rates of the other reactions, they can hardly be determined by the interference due to the mere bulk of the substituent implied by the name *steric hindrance*. The effect may better be called a *proximity effect* or an *ortho effect*.[57,59] The effect of substituents in the α-position of aliphatic compounds appears to be similar and is included in the first term.

The Relation between the Proximity Effect and the Kinetic-energy Terms.—There is a striking parallelism between the conditions which give rise to a proximity effect and those which lead to a change in entropy of reaction or of activation upon the introduction of a substituent. In general, meta and para substituents do not alter the entropy; in general, they satisfy the linear free-energy relationship. In general, ortho substituents do alter the entropy; in general, they produce a proximity effect, which is a deviation from the linear relationship. In particular, however, ortho substituents do not alter the entropy of activation of the aryl sulfuric acid hydrolysis (page 124), and this reaction (33 of Table V) also shows no proximity effect. The effect of an ortho substituent is nearly the same as that of a para substituent, and the whole series of data closely parallels that obtained in the hydrolysis of cinnamic ester in which an ortho substituent is widely removed from the point of reaction. Further, the *o*-fluo substituent does not alter the entropy of activation in the benzoic ester hydrolysis; (page 122) its effect upon the rate of the reaction closely parallels that observed in the cinnamic ester hydrolysis, that of the other halogens does not.

In the problem of orientation in ring substitutions, it has been found (page 125) that a substituent has the same effect upon the entropy of activation for reaction in the ortho position as in the other positions. It is among the most familiar facts in organic chemistry that the rate of substitution in the ortho position closely parallels that in the para position, that a substituent orients either ortho-para or meta. It is, therefore, very probable that the proximity effect acts through and is the direct result of the kinetic-energy terms in the equilibrium and rate equations and that when, in special cases, these terms vanish

[59] DIPPY, EVANS, GORDON, LEWIS, and WATSON, *J. Chem. Soc.*, 1421 (1937).

for reaction in the ortho position the rate of reaction in that position is nearly identical with that in the para position.

The kinetic-energy terms that produce the proximity effect are in some cases closely related to the interaction of the reacting substances with the solvent, because a proximity effect may appear in the action of changing solvent on a reaction. Figure 4 plots data for the relative ionization constants K/K° in the solvent butanol (page 85) against the same quantity in water.
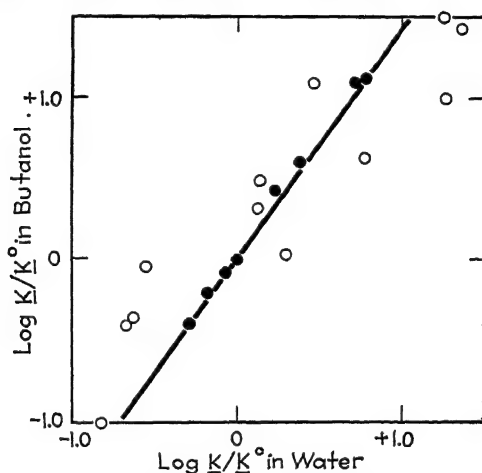
Fig. VII-4.—Relative acidity constants in water and butyl alcohol.[1*]

The full circles that represent meta and para substituted benzoic acids satisfy a linear free-energy relationship, the open circles that represent ortho-substituted benzoic acids and aliphatic acids do not. The proximity effect is very specific in its incidence. Aniline and its derivatives show it in nearly every reaction; the very similarly constituted phenolate ion does so rarely if ever.[25,26] A double ortho methyl substitution completely suppresses the ordinary carbonyl-group reactions of acetophenone and benzoic acid (page 204), yet does not interfere with the rupture by sulfuric acid to *m*-xylol and carbon dioxide or acetic acid.[60] In fact, there seems never to be any steric hindrance in reactions in which the ortho-substituted phenyl group carrying its bonding electron pair breaks loose from the rest of the molecule.

[60] Buning, *Rec. trav. chim.*, **40**, 327 (1921).

The Effect of Structure on the Reactions of Aliphatic Compounds.—The complicated phenomena that appear in the effect of structure on the reactions of aliphatic substances are not at present amenable to quantitative correlation or to theoretical interpretation except in limited fields, and they show qualitative parallelisms only when the reactions compared are of similar type (page 153).

In addition to the data already reported (page 154) the following information on nucleophilic displacements is available. The displacement of chloride ion by iodide ion (reaction 1 of Table II, Chap. V) shows the rates relative to that of ethyl chloride indicated:[61] cyclohexyl chloride, < 0.0005; chloracetone, 18,400; chloracetophenone, 54,000; $ClCH_2CN$, 1600; ethyl chloracetate, 887; CH_3OCH_2Cl, 470; ethyl chloroformate, 13; benzoyl chloride, 360; triphenylmethyl chloride, 19,600; C_6H_5—C≡C—Cl, very small; C_6H_5—C≡C—CH_2Cl, about the same as C_6H_5—CH=CH—CH_2Cl. The effect of the ring closure in cyclohexyl chloride is a specific one which appears in other reactions of ring compounds. Unsaturation of the carbonyl type produces a greater acceleration than olefinic unsaturation; in both cases the rate is greater with β than with α unsaturation (*cf.* chloracetophenone and benzoyl chloride).

The closely related displacement of iodide by thiosulfate ion (reactions 8 and 9 of Table II, Chap. V) exhibits similar effects. The relative rates of reaction of methyl iodide and of ethyl iodoacetate at 25° are as 1:8.2, those of methyl chloride, ethyl chloracetate, chloracetone, and chloracetate ion as 1:2.7:17.0:0.19. The last figure shows the expected effect of a negative charge. Halogens retard in the β-position, the rates for methyl iodide, ethylene diiodide, and ethylene bromiodide at 25° being as 1:0.42:0.26. Ethylene chloriodide and chlorbromide react by a first-order solvolytic mechanism.

The reaction of alkyl bromide with pyridine shows the following relative rates: *n*-propyl bromide, 1; benzyl bromide, 286; allyl bromide, 70; bromacetophenone, 406; ethyl bromacetate, 56.1,[62] and thus resembles the nucleophilic displacements in which the displacing group is negatively charged.

[61] Ref. 32, Chap. V, also MURRAY, *J. Am. Chem. Soc.*, **60**, 2662 (1938).
[62] CLARKE, *J. Chem. Soc.*, **97**, 416 (1910).

All known reactions of alkyl halides are faster with the iodide than the bromide and much faster with the bromide than with the chloride.

The reaction of alcohol with HBr in phenol (reaction 11 of Table II, Chap. V) exemplifies the structural effect in reactions involving an electrophilic attack on oxygen or halogen. The following relative rates at 97° are based partly upon extrapolation from lower temperatures: CH_3OH, 1; $C_6H_5OCH_2CH_2OH$, 0.00788; $C_6H_5OCH_2CH_2CH_2OH$, 0.0944; $ClCH_2CH_2OH$ and $NO_2CH_2CH_2OH$, too small to be measured; $HOCH_2CH_2OH$, 0.0139; $HOCH_2CH_2CH_2OH$, 0.1231; $HO(CH_2)_4OH$, 0.965; $HO(CH_2)_5OH$, 0.2139; $HO(CH_2)_6OH$, 0.1211. The irregularity in the effect of lengthening chain in the glycols is a not uncommon feature of such systems.[63]

Reactions involving a nucleophilic displacement on hydrogen, protolytic reactions, are affected by substitution on the α-carbon in an opposite fashion from the electrophilic displacements on oxygen or halogen. Thus the relative rates of neutralization of nitroalkyls[64]

$$R'R''CHNO_2 + OH^- \rightarrow [R'R''CNO_2]^- + H_2O \qquad (II)$$

are for nitromethane, 1; nitroethane, 0.164; nitroisopropane, 0.0087; nitro-*n*-propane, 0.123. The equilibrium constants vary in the opposite direction, being for nitromethane, 0.26×10^{-10}; nitroethane, $27. \times 10^{-10}$; nitro-*i*-propane, greater than for nitroethane. This is a most important case of the failure of the usual rate-equilibrium parallelism. The base-catalyzed bromination of acetophenone the rate-determining step of which is a similar proton transfer shows a similar structural effect,[65] the relative rates being $C_6H_5COCH_3$, 1; $C_6H_5COCH_2CH_3$, 0.154; $C_6H_5CH(CH_3)_2$, 0.0298; $C_6H_5CH_2CH_2CH_3$, 0.135; $C_6H_5COCH_2CH(CH_3)_2$, 0.059. A similar effect is noted in the base-catalyzed deuterium exchange.[66]

[63] BENNETT and MOSSES, *J. Chem. Soc.*, 2956 (1931). PALOMAA, *Ber.*, **71B**, 480 (1938). AYLING, *J. Chem. Soc.*, 1014 (1938).

[64] (*a*) JUNELL, Dis., Upsala, 1935. (*b*) MARON and LAMER, *J. Am. Chem. Soc.*, **60**, 2588 (1938).

[65] EVANS and GORDON, *J. Chem. Soc.*, 1434 (1938).

[66] IVES, *J. Chem. Soc.*, 81 (1938).

Substitution of alkyl for hydrogen on the α-carbon decreases the acidity of the proton in alcohols (page 50). Reactions that involve the displacement of this hydrogen by another group show a corresponding decrease in rate. Thus the reaction

$$\text{ROH} + p\text{-NO}_2\text{C}_6\text{H}_4\text{COCl} \rightarrow p\text{-NO}_2\text{C}_6\text{H}_4\text{COOR} + \text{HCl} \qquad \text{(III)}$$

shows the following relative rates in ether at 25°:[67] with R = CH$_3$, 1; C$_2$H$_5$, 0.459; i-C$_3$H$_7$, 0.0549; t-C$_4$H$_9$, 0.0147; n-C$_3$H$_7$, 0.358; i-C$_4$H$_9$, 0.167; n-C$_4$H$_9$, 0.382; C$_6$H$_5$, 0.0929; C$_6$H$_5$CH$_2$, 0.217. For the reaction[68]

$$\text{ROH} + \text{C}_6\text{H}_5\text{NCO} \rightarrow \text{ROCONHC}_6\text{H}_5 \qquad \text{(IV)}$$

in benzene at 26° the relative rates are as follows: CH$_3$, 1; C$_2$H$_5$, 0.96; i-C$_3$H$_7$, 0.31; t-C$_4$H$_9$, 0.0032; n-C$_3$H$_7$, 0.78; i-C$_4$H$_9$, 0.69; n-C$_4$H$_9$, 0.97.

No reaction has been more widely investigated from the structural point of view than the ionization of carboxylic acids. Recent accurate values[69] of the ionization constant times 10^5 of RCOOH in water at 25° are as follows: R = H, 17.72; CH$_3$, 1.76; C$_2$H$_5$, 1.34; i-C$_3$H$_7$, 1.38; t-C$_4$H$_9$, 0.891; n-C$_3$H$_7$, 1.50; i-C$_4$H$_9$, 1.67; n-C$_4$H$_9$, 1.38; n-C$_5$H$_{11}$, 1.32; CH$_2$=CH, 5.501; ClCH$_2$, 137.9; HOCH$_2$, 14.76; C$_6$H$_5$, 6.27; C$_6$H$_5$CH$_2$, 4.88; CH$_3$C≡C, 222.8.

It is a well-known qualitative fact that the addition reactions of carbonyl compounds go faster with aldehydes than with ketones and faster with methyl ketones than with others. This is borne out by the quantitative data of Table VI on the rate of formation of semicarbazones at 25° in an aqueous phosphate buffer of pH 7.

The wide differences between the effects of changing structure upon the rate of the formation, the rate of the reverse reaction of hydrolysis, and the equilibrium constant of the reaction show again that the rate-equilibrium parallelism is no general law free of restriction or limitation. The effect of such a conflict between rate and equilibrium effects is strikingly illuminated by an experiment[70a] in which a mixture of equimolar quantities

[67] Norris and Ashdown, *J. Am. Chem. Soc.*, **47**, 837 (1925).

[68] Davis and Farnum, *J. Am. Chem. Soc.*, **56**, 883 (1934).

[69] Dippy, *J. Chem. Soc.*, 1222 (1938). German, Jeffery, and Vogel, *J. Chem. Soc.*, 1604 (1937). Ref. 11, Chap. III.

of cyclohexanone, furfural, and semicarbazide yields almost pure cyclohexanone semicarbazone when worked up after a few seconds but equally pure furfural semicarbazone after a few hours. The explanation follows from the data of Table VI. Cyclohexanone reacts about fifty times as fast as furfural, but

TABLE VI.—SEMICARBAZONE REACTIONS[70]

	Rate constant for		Equilibrium constant for formation
	Formation	Hydrolysis	
Acetaldehyde............	6.02	1.73×10^{-4}	3.4×10^4
Benzaldehyde............	0.0342	1.03×10^{-7}	3.3×10^5
Furfural................	0.0122	0.92×10^{-7}	1.32×10^5
$(CH_3)_3CCHO$............	0.333	6.2×10^{-6}	5.4×10^4
$CH_3CCOCOOH$.........	0.1229	6.3×10^{-7}	1.96×10^5
Acetone................	0.1004	3.0×10^{-4}	309
Cyclohexanone.........	0.600	1.27×10^{-3}	467
$(CH_3)_3CCOCH_3$.........	0.00113	1.43×10^{-5}	79

the equilibrium constant for the formation of its semicarbazone is only one-three hundredth of that of the aldehyde. Consequently, the more rapidly formed ketone derivative is, in the course of time, converted almost entirely into the more stable aldehyde compound.

More approximate data on the rates of formation of phenylhydrazones and bisulfite derivatives[71] parallel those obtained in the semicarbazone formation. The equilibrium constants of the cyanhydrine reaction[72] do not parallel the rates of the other carbonyl reactions.

The alkaline ester hydrolysis in water solution[73] shows the following relative rates at 25°: For CH_3COOR with $R = CH_3$, 1; C_2H_5, 0.601; $i\text{-}C_3H_7$, 0.146; $t\text{-}C_4H_9$, 0.0084; $n\text{-}C_3H_7$, 0.549; $CH_2{=}CH$, 57.7; C_6H_5, 7.63; $C_6H_5CH_2$, 1.10; $HOCH_2CH_2$, 1.52.

[70] (a) CONANT and BARTLETT, *J. Am. Chem. Soc.*, **54**, 2881 (1932). (b) WESTHEIMER, *ibid.*, **56**, 1962 (1934).

[71] PETRENKO-KRITSCHENKO, *Ann.*, **341**, 150 (1905). STEWART, *J. Chem. Soc.*, **87**, 185 (1905).

[72] LAPWORTH and MANSKE, *J. Chem. Soc.*, 2533 (1928); 1976 (1930). ·

[73] SKRABAL *et al.*, *Monatsh.*, **45**, 148 (1924); **47**, 17; 30 (1926); **48**, 459 (1927); **50**, 369 (1928). PALOMAA, *Ber.*, **71B**, 480 (1938).

For $RCOOCH_3$ with R = H, 223; CH_3, 1; $ClCH_2$, 761; Cl_2CH, 16,000; CH_3OOC, 170,000; ^-OOC, 8.4; CH_3OOCCH_2, 13.7; $^-OOCCH_2$, 0.19. For $RCOOC_2H_5$ with R = CH_3, 0.601; C_2H_5, 0.553; CH_3CO, 10,000; CH_3COCH_2, 2.66; $HOCH_2$, 6.08; CH_3OCH_2, 11.9; $C_2H_5OCH_2$, 6.03. For the reaction of $RCOOC_2H_5$ in 87.83 per cent ethanol at 30° the relative rates are as follows:[3b,d] CH_3, 1; C_2H_5, 0.470; $i\text{-}C_3H_7$, 0.100; $t\text{-}C_4H_9$, 0.0105; $n\text{-}C_3H_7$, 0.274; $n\text{-}C_4H_9$, 0.262; C_6H_5, 0.1019; $C_6H_5CH_2$, 1.322; $C_6H_5CH{=}CH$, 0.220. Qualitative data[74] on such substances as (*E*) and (*F*) show that accumulation of alkyl groups on the β-carbon retards strongly. The most notable effects in the
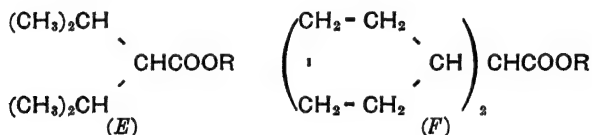
ester hydrolysis are the retardation produced by substitution of alkyl for hydrogen in either alcohol or acid component, the low rate of reaction of benzoic esters, and the acceleration produced by electron-attracting substituents.

The addition of the Grignard reagent to esters is affected by the structure of the ester in a way which strikingly parallels that observed in the ester hydrolysis. The rate is several orders of magnitude smaller for *t*-butyl benzoate than for methyl benzoate with the ethyl and *i*-propyl esters in order, relatively low for benzoate as compared with acetate, and very low for trimethyl acetate and for ortho-substituted benzoates.[75]

In the acid-catalyzed esterification of carboxylic acids, the relative rates are as follows:[76] for the HCl-catalyzed reaction of $RCOOH$ in ethanol at 14.5° with R = CH_3, 1; C_2H_5, 0.83; $i\text{-}C_3H_7$, 0.54; $t\text{-}C_4H_9$, 0.025; $C_6H_5CH_2$, 0.56; $(C_6H_5)_2CH$, 0.0153; $(C_6H_5)_3C$, negligible; $ClCH_2$, 0.66; Cl_2CH, 0.0175; Cl_3C, 0.0101; $BrCH_2$, 0.54; Br_2CH, 0.0139; Br_3C, 0.0037; $(CH_3)_2CBr$, 0.037;

[74] v. BRAUN and FISCHER, *Ber.*, **66B**, 101 (1933).

[75] VAVON, BARBIER, and THIEBAUT, *Bull. soc. chim.* [5], **1**, 806 (1934).

[76] SUDBOROUGH and LLOYD, *J. Chem. Soc.*, **75**, 467 (1899). SUDBOROUGH and TURNER, *ibid.*, **101**, 237 (1912). HINSHELWOOD and LEGARD, *ibia.*, 1588 (1935).

CH_3CBr_2, 0.0066. Similar experiments in methanol yielded parallel results and the additional information that the relative rates of esterification of phenylacetic and benzoic acid are as 1:0.0053. Accumulation of alkyl on the β-carbon retards this reaction[74] as it does the alkaline hydrolysis.

The equilibrium constant of the esterification is only slightly affected by the structure of the acid or the alcohol.[77] Structural changes that alter the rate of reaction by several orders of magnitude shift the equilibrium constant by only a few per cent, and the largest change in the latter constant on record is the 50 per cent difference between acetic and formic acids.[77c]

The effect of a substituent on the rate of the acid-catalyzed hydrolysis must, therefore, be nearly identical with its effect on the rate of esterification. Some pertinent data follow.[73] For the hydrolysis of CH_3COOR in water at 25° with R = CH_3, 1; C_2H_5, 0.97; i-C_3H_7, 0.53; t-C_4H_9, 1.15; n-C_3H_7, 1.00; CH_2=CH, 1.20; C_6H_5, 0.69; $C_6H_5CH_2$, 0.96; $HOCH_2CH_2$, 0.70; CH_3CH= CH, 0.70. For the hydrolysis of $RCOOCH_3$ in water at 25°, H, 21.3; CH_3, 1.00; CH_3OOC, 1.71; $HOOC$, 0.85; $CH_3OOCCH_2CH_2$, 0.35; CH_3CO, 1.20; CH_3COCH_2, 0.157; $CH_3COCH_2CH_2$, 0.23. For the hydrolysis of $RCOOC_2H_5$ in 60 per cent by volume ethanol at 60°,[78] CH_3, 1; $ClCH_2$, 0.911; Cl_2CH, 0.397; Cl_3C, 0.1120; C_6H_5, 0.00577.

The small effect produced by changes in the structure of the alcohol component is in notable contrast to the large one observed in the alkaline hydrolysis. With respect to the structure of the acid component the two reactions differ in a way that suggests the following interpretation, which is also consistent with the effect of substituents in the benzene ring on the same reactions. In the alkaline hydrolysis the electron displacement effect is large ($\rho = 2.498$), with ortho or α substituents the proximity effect modifies it to a relatively small degree; in the acid-catalyzed reactions the electron displacement effect is small ($\rho = -0.467$), but the proximity effect is very large.

[77] (a) MENSCHUTKIN, *Ann.*, **195**, 334; **197**, 193 (1879). (b) LICHTY, *Am. Chem. J.*, **18**, 590 (1896). (c) KISTIAKOWSKI, *Z. physik. Chem.*, **27**, 250 (1898). (d) BRANCH and McKITTRICK, *J. Am. Chem. Soc.*, **45**, 321 (1923).

[78] TIMM and HINSHELWOOD, *J. Chem. Soc.*, 862 (1938).

In the reactions of acid chlorides the relative rates of the alcoholysis of RCOCl in 60 per cent ether 40 per cent ethanol at 25° are[31] for R = CH_3, 1; $ClCH_2$, 20.2; Cl_2CH and Cl_3C, over 30; C_6H_5, 0.005. The relative rates of reaction of RCOCl with β-chlorethanol in dioxane at 25° are[79] for R = CH_3, 1; C_2H_5, 0.784; i-C_3H_7, 0.74; t-C_4H_9, 0.109; n-C_3H_7, 0.96; i-C_4H_9, 0.88; CH_3OCH_2, 0.446; $ClCH_2$, 1.48; Cl_2CH, 4.46; Cl_3C, 33; CH_2ClCH_2, 0.285.

The Effect of the Solvent upon Reactivity.—The effect of the medium in which a reaction occurs upon its rate and equilibrium may be as profound as that of a change in the structure of the reactant. Some generalizations of limited range are possible. Reactions involving ions require a medium of reasonably high polarity (page 130). The solvent is a reactant in the ionization of acids or bases and affects the reaction both for this reason and because a change in solvent implies a change in medium. The relative extent of the ionization of two acids depends, however, only on the medium effect and appears to be primarily a function of the dielectric constant (page 81). The attempt is often made to relate the rate or equilibrium of other reactions to the dielectric constant of the medium, but the apparent agreement sometimes found depends upon a limited choice of solvents. Thus the relative rates of reaction of pyridine and ethyl iodide

$$C_5H_5N + C_2H_5I \rightarrow [C_5H_5NC_2H_5]^+ + I^- \qquad (V)$$

in various solvents[80] are given in Table VII along with the dielectric constant of the solvent.

The rates in the alcohol solvents lie in the order of the dielectric constants as do many others of their properties, but nitrobenzene and acetone fall out of line completely. Indeed the dielectric-constant hypothesis may be in even more serious difficulty than these data indicate. Apparently,[81] reactions of this type have as their rate-determining step in nonpolar solvents the crystallization of the salt rather than the formation of the ions. The rate of the latter process may, therefore, be considerably greater than the over-all rate of reaction given in the table.

[79] LEIMU, *Ber.*, **70B**, 1040 (1937).
[80] NORRIS and PRENTISS, *J. Am. Chem. Soc.*, **50**, 3042 (1928).
[81] EDWARDS, *Trans. Faraday Soc.*, **33**, 1294 (1937).

The effect of water upon reactions in alcohol medium is generally that predicted from the increase in dielectric constant which it produces,[32] the effect of other solvents is not (page 168).

TABLE VII.—THE SOLVENT EFFECT IN THE PYRIDINE ETHYL IODIDE REACTION

Solvent	Relative rate	Dielectric constant (20°)
Nitrobenzene	25.0	35.8
Acetone	12.8	19.6
Methanol	2.50	32.4
Ethanol	1.40	25.0
n-Propyl alcohol	1.11	20.81
n-Butyl alcohol	1.11	
i-Propyl alcohol	1.07	18.62
Benzene	1.	2.28
t-Butyl alcohol	0.93	3.76

Relationships between Closely Similar Reactions.—Complicated, even confusing as the effects of structure on reactivity seem, they nevertheless permit two important generalizations. (1) Similar changes in structure have similar effects upon related reactions, and the similarity of effect increases with the resemblance of the reactions. (2) This requirement is less rigid when the changes in structure occur at a point in the molecule widely separated from the reacting group. The qualitative similarity of effect goes over to the quantitative linear free-energy relationship when the distance between substituent and reacting group is large and other requirements, present in benzene derivatives and probably due to their rigidity of structure, are satisfied. The quantitative relationship may also appear without these limitations when the reactions compared are very much alike The typical case of a relationship of this sort and the prototype of all linear free-energy relationships is the Brønsted catalysis law.

General Acid and Base Catalysis: The Nitramide Reaction.— In its earliest days, the ionic theory set up the hypothesis that the rate of an acid- or base-catalyzed reaction is proportional to the concentration of hydrogen or of hydroxyl ion, respectively.

[32] HUGHES, *Trans. Faraday Soc.*, **34**, 196 (1938).

Except for minor complications due to salt effect, which are not, however, very important in most reactions of this sort, the hypothesis is satisfactorily verified by many reactions, notably in the sucrose inversion and in the diazoacetic ester decomposition. The decomposition of nitramide shows, however, strikingly different properties.[83]   The reaction

$$H_2N_2O_2 \rightarrow H_2O + N_2O \qquad (VI)$$

is catalyzed to a very minor extent by acids[84] but so strongly by bases that the decomposition is practically instantaneous at sodium hydroxide or even at carbonate alkalinities.   The rate is proportional to the concentration of nitramide, so that the first-order constant or specific rate

$$k = -\frac{1}{[H_2N_2O_2]}\frac{d[H_2N_2O_2]}{dt} \qquad (12)$$

is an exact measure of the catalytic effect.

The rate is erratic and unreproducible in water but becomes steady and nearly independent of the acid concentration when small amounts of strong acid are added.   The average value of k in solutions of HCl varying from 0.001 to 0.1M is 0.63×10^{-5} sec.$^{-1}$.   This quantity measures an "uncatalyzed" reaction or more properly one catalyzed by the solvent water.   In acetate buffer solutions an entirely new phenomenon, a catalysis by acetate ion, appears, as the data of Table VIII demonstrate.

TABLE VIII.—NITRAMIDE CATALYSIS IN ACETATE BUFFERS[83]

Experi-ment	$NaC_2H_3O_2$	$HC_2H_3O_2$	μ	10^5k	10^3k_c
1	0.00407	0.0162	0.02	4.10	8.38
2	0.00679	0.0135	0.02	6.37	8.40
3	0.00679	0.0135	0.1	6.37	8.39
4	0.0102	0.0101	0.02	9.18	8.38
5	0.0136	0.0067	0.02	12.10	8.43

The solutions contained the stoichiometric concentrations of sodium acetate and acetic acid listed, together with enough

[83] Brønsted and Pedersen, *Z. physik. Chem.*, **108**, 185 (1924).
[84] Marlies and LaMer, *J. Am. Chem. Soc.*, **57**, 1812 (1935).

sodium chloride to bring the ionic strength μ to the value shown. It is obvious that there is a pronounced increase in rate over that of the water reaction, that the increase is not produced by the acetic acid, and that it is not a salt effect. The catalytic constant k_c, given by

$$k = 0.63 \times 10^{-5} + k_c[C_2H_3O_2{}^-] \qquad (13)$$

is satisfactorily constant, which implies that the rate in these solutions is the sum of that of the water reaction plus that of an acetate ion catalyzed reaction the rate of which is proportional to the concentration of the acetate ion. k_c is, therefore, a second-order constant for the reaction of nitramide with acetate ion.

TABLE IX.—NITRAMIDE CATALYSIS IN BENZOATE BUFFERS

Experiment	$C_6H_5CO_2Na$	$C_6H_5CO_2H$	10^5k	10^3k_c
1	0.0225	0.0125	7.76	3.16
2	0.0167	0.00830	5.92	3.17
3	0.01125	0.00625	4.30	3.26
4	0.00750	0.00375	2.90	3.01

An even more characteristic effect appears in some experiments run in benzoate buffers and listed in Table IX. In these the ratio $[C_6H_5COOH]/[C_6H_5COO^-]$ is practically constant (0.50 to 0.56). By the law of equilibrium $[C_6H_5COO^-][OH_3{}^+]/[C_6H_5COOH] = K$ the concentration of oxonium ion must be constant within the same precision except for the small salt effect. By the relation $[OH_3{}^+][OH^-] = K_w$ the hydroxyl-ion concentration must be constant also. The catalytic effect is, therefore, due neither to "hydrogen" nor to hydroxyl ion; the constancy of k_c, defined as in equation (13), shows that benzoate ion is the catalyst.

Further investigation has shown that the anions of many other acids have the same property, the catalytic constant being smaller, the stronger the acid, *i.e.*, the weaker the affinity of the ion for protons. A similar situation appears[85] when buffers of the nature of aniline-aniline hydrochloride are used; aniline is a catalyst, anilinium ion is not.

[85] BRØNSTED and DUUS, *Z. physik. Chem.*, **117**, 299 (1925).

Since the only property that hydroxyl ion, water, acetate ion, and aniline have in common is an affinity for protons and since all substances possessing this affinity are catalysts, the proton affinity is most probably responsible for the catalytic effect. In fact, it was as a result of the discovery of this phenomenon that the proposal was first made that the name *base* be generalized to include all substances with a proton affinity (page 48). A catalysis of the type found in the nitramide reaction is called a *general base catalysis, i.e.,* a catalysis by all bases and not merely by hydroxyl ion alone. The complete expression for the rate of the nitramide decomposition is, therefore,

$$- \frac{d[H_2N_2O_2]}{dt} = \sum^{i} k_i[B_i][H_2N_2O_2] \tag{14}$$

or

$$k = \sum^{i} k_i[B_i] \tag{15}$$

with B_i any base and k_i the corresponding catalytic constant. The summation is taken over all the bases present including the solvent.

A General Acid Catalysis: Hydrolysis of Ethyl Orthoacetate.— In this reaction[86]

$$CH_3C(OC_2H_5)_3 + H_2O \rightarrow CH_3COOC_2H_5 + 2C_2H_5OH \tag{VII}$$

TABLE X.—CATALYSIS IN THE HYDROLYSIS OF ETHYL ORTHOACETATE

Concentration		Ratio [A]/[B]	$10^4 k$
Sodium salt, B	*m*-Nitrophenol, A		
0.0202	0.0202	1.00	1.44
0.0160	0.0160	1.00	1.35
0.00566	0.00566	1.00	1.20
0.00242	0.00242	1.00	1.21
0.0135	0.0183	1.36	1.77
0.00756	0.01025	1.36	1.61
0.00284	0.00384	1.36	1.54
0.0145	0.0309	2.13	2.84
0.00483	0.0103	2.13	2.47
0.00145	0.0031	2.13	2.37

[86] BRØNSTED and WYNNE-JONES, *Trans. Faraday Soc.* **25**, 59 (1929).

there is no appreciable catalysis by bases, the rate having the same small value 1×10^{-8} in 0.5N and 0.1N sodium hydroxide. The data of Table X show the specific rates observed at 20° in buffer solutions of *m*-nitrophenol and its sodium salt together with enough sodium chloride to maintain an ionic strength of 0.05.

Even when the ratio nitrophenol over nitrophenolate ion and, hence, the oxonium-ion concentration is constant, the rate
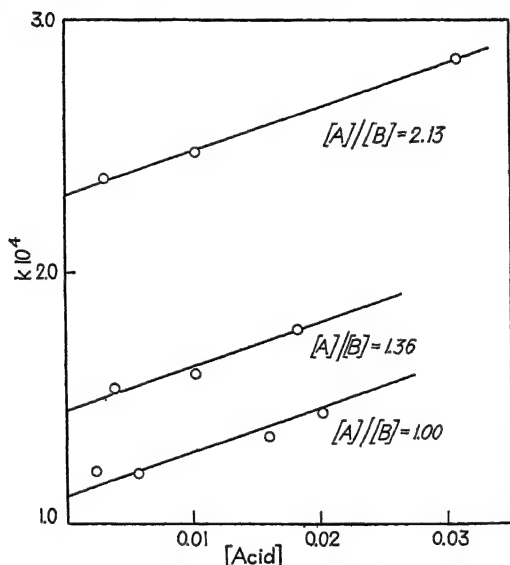
Fig. VII-5.—Variation of specific rate of hydrolysis of ethyl orthoacetate with acid concentration in *m*-nitrophenolate buffers.[86]

decreases with decreasing acid concentration. As Fig. 5 shows, the specific rate at any given oxonium-ion concentration varies linearly with the concentration of the catalyzing acid; however, the intercept at zero acid concentration is not zero but has a value that is proportional to the concentration of oxonium ion. These results require an expression of the form

$$k = k_w + k_H[\text{OH}_3^+] + k_a[\text{NO}_2\text{C}_6\text{H}_4\text{OH}] \qquad (16)$$

or more generally

$$k = \sum^i k_i[\text{A}_i] \qquad (17)$$

k_w the spontaneous or water-catalyzed rate is in fact negligible; k_a the catalytic constant for m-nitrophenol is given by the slope of the lines in Fig. 5 and has a value of 0.0017; k_H the catalytic constant for oxonium ion is given by the ratio of the intercept of each line to the corresponding oxonium concentration and is found to be 1.09 $\pm$ 0.02 times the ionization constant of m-nitrophenol. In the general formula A_i is any acid, including water and oxonium ion, and k_i is the corresponding catalytic constant.

The experimental investigation of the orthoacetate catalysis is more difficult than that of the nitramide reaction because it is not possible to find buffers in which catalysis due to the oxonium ion is negligible, as is that of hydroxyl ion in acetate buffers in the nitramide case. The hydrolysis of ethyl orthopropionate and that of ethyl orthocarbonate show a general acid catalysis of the same sort as that of the orthoacetate.

A Specific Oxonium-ion Catalysis.—The hydrolysis of ethyl orthoformate shows a rate which, except for a pronounced salt effect, is determined solely by the concentration of oxonium ion.[86]

TABLE XI.—CATALYSIS IN THE HYDROLYSIS OF ETHYL ORTHOFORMATE[86]

Concentration		[A]/[B]	$10^4 k$	$10^4 k$[B]/[A]
Sodium caco-dylate [B]	Cacodylic acid [A]			
0.025	0.0242	0.938	5.11	5.45
0.0129	0.0121	0.938	5.11	5.45
0.00645	0.00605	0.938	5.15	5.49
0.0336	0.0164	0.488	2.57	5.27
0.0168	0.0082	0.488	2.57	5.27
0.0400	0.0100	0.250	1.34	5.36
0.0040	0.0010.	0.250	1.42	5.68

Table XI presents data in cacodylic acid-sodium cacodylate buffers at 20° and an ionic strength of 0.05. A fourfold increase in the concentration of cacodylic acid produces no measurable change in rate provided the concentration of sodium cacodylate is increased in the same proportion so that the oxonium-ion concentration remains constant. When the oxonium-ion concentration is altered by a change in the buffer ratio, the rate changes proportionally as the constancy of the ratio in the last

column of the table demonstrates. This is equal to the ratio of rate to oxonium-ion concentration multiplied by the ionization constant of cacodylic acid.

The rate law for this reaction is, therefore,

$$- \frac{d[\text{ester}]}{dt} = k[\text{ester}][\text{OH}_3{}^+] \tag{18}$$

and the only effective catalyst is oxonium ion. Such a reaction is said to be subject to a *specific oxonium-ion catalysis* in contrast to the general acid catalysis of the orthoacetate reaction. The *criterion of distinction between a specific oxonium-ion catalysis and a general acid catalysis is the behavior of the rate when the concentration of both components of a buffer solution is increased in the same proportion and at constant ionic strength.* If the rate remains unchanged, the catalysis is of the specific oxonium-ion type; if it increases, it is of the general acid type. An obvious criterion of the same sort distinguishes specific hydroxyl-ion catalysis from general base catalysis. The hydrolysis of acetal, $\text{CH}_3\text{CH}(\text{OC}_2\text{H}_5)_2$, is likewise subject to specific oxonium-ion catalysis.

Both General Acid and General Base Catalysis: The Mutarotation of Glucose.[87]—This reversible reaction, the sum of whose constants for forward and reverse reaction may be determined by the method of page 103 from optical rotation or dilatometer measurements, is catalyzed both by acids and by bases. Measurements at 18° in water, slightly acid from the carbon dioxide impurity, and in solutions of strong acids varying from 10^{-5} to 0.04M in the presence and in the absence of added salt up to 0.2M satisfy the equation

$$k = 0.000088 + 0.00242[\text{OH}_3{}^+] \tag{19}$$

The first term on the right represents the catalysis by water, the second that by oxonium ion. The latter becomes negligible when $[\text{OH}_3{}^+] < 10^{-4}$. A similar determination of the catalytic constant of hydroxyl ion is impossible because the rates are too rapid for measurement in sodium hydroxide solutions, but an upper limit of 100 may be set from measurements of the rate

[87] Brønsted and Guggenheim, *J. Am. Chem. Soc.*, **49**, 2554 (1927).

in ammonia buffers. Consequently, hydroxyl-ion catalysis becomes negligible when the hydroxyl-ion concentration is less than 10^{-8}, *i.e.*, when the pH is less than 6.

If, therefore, a buffer solution the pH of which lies in the range from 4 to 6 shows a rate greater than that of the water reaction, the effect must be due to catalysis either by the acid or the base of the buffer or by both. The experimental data show that both acetic acid and acetate ion have a pronounced catalytic effect in an acetate buffer and satisfy the equation

$$k = 0.000088 + 0.000040[\text{HA}] + 0.00044[\text{A}^-] \qquad (20)$$

The halogenation of ketones also shows both general acid and general base catalysis.[88]

The Brønsted Catalysis Law.—This is a linear free-energy relationship involving the catalytic constants of a series of acids or bases and the equilibrium constants that measure the acid or base strength of the catalysts. In the catalysis of nitramide by the ions of carboxylic acids, these basicity constants K_b are the equilibrium constants of the reactions

$$\text{RCOO}^- + \text{OH}_3^+ \rightleftharpoons \text{RCOOH} + \text{H}_2\text{O} \qquad \text{(VIII)}$$
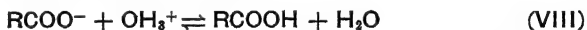
and are, consequently, the reciprocals of the ionization constants of the acids RCOOH. In Fig. 6 the logarithms of the catalytic constants k_c for the nitramide reaction are plotted against the basicity constants of the catalysts. The open circles which refer to carboxylate ions lie on the best straight line shown with a median deviation of 0.018, which corresponds to a probable error in k_c of 4 per cent. The experimental data are probably no more accurate than this.

Bases conjugate to dibasic acids, such as acid succinate ion, would deviate from this line considerably if a statistical correction were not made. This may be derived from the principle that K_b is not in this case a correct measure of the proton affinity of the base, because the base may be formed from the acid (succinic acid) in two equivalent ways, *viz.*, by the ionization of the proton from the one or from the other carboxyl group.

[88] Dawson and Carter, *J. Chem. Soc.*, 2282 (1926). Dawson, Hall, and Key, *ibid.*, 2844 (1928). Dawson, Haskins, and Smith, *ibid.*, 1884 (1929).

The ion has, therefore, twice as good a chance of being formed as corresponds to the work needed to remove the proton, and the correct measure of the work is, therefore, not K_a but $\frac{1}{2}K_a$. By the same token, the measure of the basicity of the ion is not K_b but $2K_b$. The ringed circles in Fig. 6 refer to bases of this type and are plotted with the quantity $2K_b$ as the abscissa. The median deviation from the line of the points thus plotted is only
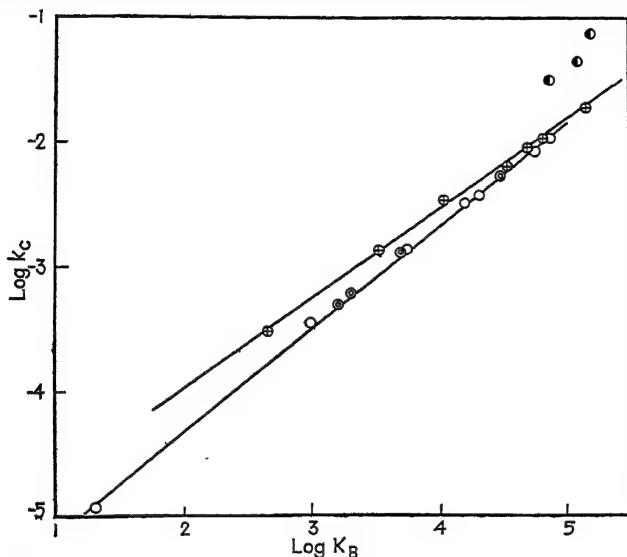
Fig. VII-6.—Comparison of catalytic constants k_c with basicity constants K_b in the nitramide catalysis. ○ carboxylate ions derived from monobasic acids; ◎ singly charged carboxylate ions derived from dibasic acids; ⊕ nuclear substituted anilines; ◗ other amine bases.

0.012; if the statistical correction had not been made, they would lie 0.3 unit to the left of the line.

When the catalyst is an amine, the measure of basicity K_b is the equilibrium constant of the equation

$$RNH_2 + OH_3^+ \rightleftharpoons RNH_3^+ + H_2O \qquad (IX)$$
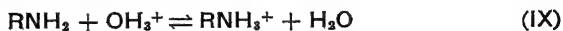
which is easily shown (page 255) to be equal to the ionization constant of the base divided by the ion product constant of water. The crossed circles in Fig. 6 refer to aniline, the three toluidines, and the three chloranilines. These also lie on a straight line with a median deviation of 0.025, but it is a different

line from that determined by the carboxylate ions and has a slope of 0.72 instead of 0.82.

Data for bases of other types, such as doubly negative carboxylate ions and positively charged hydroxometallic ions, lie on still other lines.

These straight lines, the equations of which are of the form

or

$$\left.\begin{array}{c} \log k_c = x \log K_b + C \\[2mm] k_c = G K_b^x \end{array}\right\} \tag{21}$$

are obviously linear free-energy relationships, but for the following reason they involve the rate and the equilibrium of the same series of reactions rather than the constants for different reactions. The catalytic reactions must involve some such sequence as

$$H_2N_2O_2 + B \rightarrow HN_2O_2^- + BH^+ \tag{X}$$

$$HN_2O_2^- \rightarrow N_2O + OH^- \tag{XI}$$

$$OH^- + BH^+ \rightleftharpoons B + H_2O \tag{XII}$$
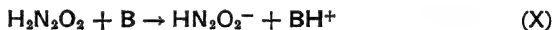
with the first step rate determining. The catalytic constant is, therefore, the rate constant of the proton transfer (X). The basicity constants for a series of bases B must, however, be proportional to the equilibrium constants for the same series of reactions [(X)], the proportionality constant being the equilibrium constant of the reaction

$$OH_3^+ + HN_2O_2^- \rightleftharpoons H_2O + H_2N_2O_2 \tag{XIII}$$
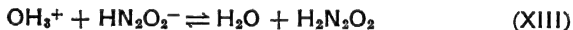
The proportionality constant may be absorbed into the C or G of equation (21), converting this into a relation between the rate constants and the equilibrium constants of reaction (X).

The Range of Permissible Change in Structure.—With this close similarity in the series of constants involved in the linear relationship, a much wider latitude in the structural variations is permissible. Ortho-substituted anilines lie on the same line as meta and para derivatives, and benzoate and acetate ions and their derivatives conform to a single relationship. There are however limits; the structural change must not extend to a complete alteration in the nature of the reacting group in the catalyst. The carboxylate ions do not lie on the same line as the aniline derivatives, but the difference does not seem to be the

result of the difference in electrical charge. Thus pyridine, quinoline, and dimethylaniline, all electrically uncharged bases, fail to conform to the line established by aniline derivatives,[33] as the shaded circles in Fig. 6 show, and no reasonable statistical correction brings them into line. It appears, therefore, that the conversion of a primary to a tertiary amine is not a permissible variation in the structure of the catalyst if the linear relation is to hold.[89] On the other hand, bases of the types CH_3COO^-, $^+H_3NCH_2COO^-$, $^-OOCCHNH_3^+CH_2COO^-$, $^+H_3N(CH_2)_4CHNH_3^+COO^-$ in which the charge varies from -1 to $+1$, but in which the reacting group (the COO^-) is constant, show no systematic effect of charge.[90] Furthermore, the failure of any parallelism to appear between the rate and the equilibrium of the ionization of nitromethane derivatives (page 209) shows how fatal a structural change in the immediate neighborhood of the reacting group is to even a qualitative relation between rate and equilibrium. The nitromethane case is, in fact, a close analogue of the primary-tertiary amine discrepancy in the nitramide catalysis.

The change from a carboxylate anion to such inorganic ions as acid phosphate or sulfate seems to be permissible. This is not inconsistent with the structures (G) and (H)

$$\left[\begin{array}{c} R - C \vcenter{.}. \ddot{O}\,\cdot \\ \cdot \ddot{O} \\ \bar{} \end{array} \right]^- \qquad \left[\begin{array}{cc} \cdot \ddot{O} & \ddot{O}\cdot \\ & S \\ \cdot \ddot{O} & \ddot{O}\cdot \end{array} \right]^-$$

$$(G) \qquad\qquad (H)$$
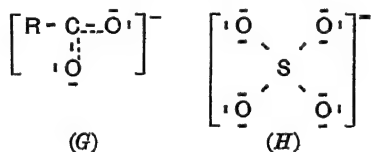
for the atom to which the proton becomes attached is oxygen in each case, and the nature of the rest of the molecule in the immediate vicinity is not too different. A statistical factor is, of course, necessary in view of the two oxygens in the one case and the four in the other. On the other hand, the agreement of points for water and oxonium ion, which appears in some but not in all cases, can hardly be the result of anything but coincidence.

[89] This conclusion is supported by unpublished data reported by Pfluger at the Baltimore meeting of the American Chemical Society, April, 1939.

[90] WESTHEIMER, *J. Org. Chem.*, **2**, 431 (1937).

A comparison of the rate constants of two base-catalyzed reactions permits an even wider range of variation in the structure of the catalyst than does the comparison of the rate and equilibrium constants for a single reaction series. When the

TABLE XII.—DATA ON THE BRØNSTED CATALYTIC LAW

Reaction	Catalyst type and number	r	C	x
Nitramide, H_2O, 15°[83,85]	$RCOO^-$, 11	0.016	−5.964	0.822
Nitramide, H_2O, 15°	$XC_6H_5NH_2$, 7	0.025	−5.418	0.718
Nitramide, cresol, 20°[92]	$RCOO^-$, 12	0.07	......	0.78
Nitramide, cresol, 20°[92]	$XC_6H_5NH_2$, 7	0.06	......	0.84
Glucose mutarotation H_2O, 18°[87]	$RCOO^-$, 13	0.051	−5.054	0.359
Glucose mutarotation H_2O, 18°[87]	RCOOH, 8	0.040	−3.120	0.269
Acetone iodination H_2O, 25°[88]	RCOOH, 7	0.046	−4.467	0.622
Acetone iodination H_2O, 25°[88]	$RCOO^-$, 3	.....	−3.93	0.83
$(C_2H_5O)_2PHO + I_2$, H_2O, 20°[93]	RCOOH, 4	.....	−7.52	0.99
Acetacetic ester $+Br_2$, H_2O, 25°[94]	$RCOO^-$, 3	.....	−3.16	0.60
Bromacetacetic ester $+Br_2$, H_2O, 25°[94]	$RCOO^-$, 3	.....	−1.19	0.65
Diazoacetate ion decomp. H_2O, 25°[95]	various, 7	.....	......	0.83
Nitromethane ionization H_2O, 20°[96]	$RCOO^-$, 3	.....	−7.50	0.67
Nitromethane ion + HA, H_2O, 0.05°[64a]	RCOOH, 5	.....	+2.16	0.37
Nitroethane ion + HA, H_2O, 0.05°	RCOOH, 5	.....	−0.76	0.37
Dihydroxyacetone depolymerization, H_2O, 25°[97]	$RCOO^-$, 7	0.069	−5.792	0.777
Dihydroxyacetone depolymerization, H_2O, 25°[97]	RCOOH, 4	0.043	−1.570	0.555

logarithms of the catalytic constants for the base-catalyzed glucose mutarotation are plotted against those for the nitramide reaction, a single straight line suffices for data on a variety of catalysts that require several lines for the expression of the Brønsted law.[91]

[91] PFLUGER, *J. Am. Chem.*, **60**, 1513 (1938).

[92] BRØNSTED, NICHOLSON, and DELBANCO, *Z. physik. Chem.*, **A169**, 379 (1934).

[93] NYLEN, Dis., Upsala, 1938.

[94] PEDERSEN, Dis., Copenhagen, 1932; *J. Phys. Chem.*, **38**, 601; 999 (1934).

[95] KING and BOLLINGER, *J. Am. Chem. Soc.*, **58**, 1533 (1936).

[96] PEDERSEN, *Kgl. Danske Videnskab. Selskab, Math.-fys. Medd.*, **12**, No. 1 (1932).

[97] BELL and BAUGHAN, *J. Chem. Soc.*, 1947 (1937).

Data on Catalytic Reactions.—Table XII lists the available data on the application of the Brønsted law. The quantities C and x are those of equation (21), and r, the probable error, measures the precision with which the law applies.
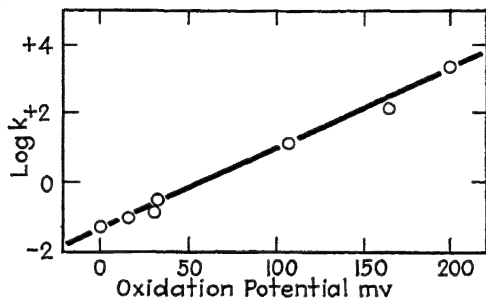
FIG. VII-7.—Comparison of specific rates and oxidation potentials in the reduc- • tion of quinones.[1a,99]
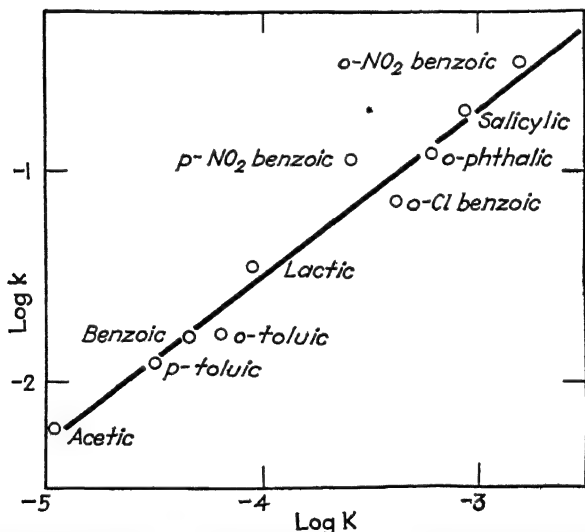
FIG. VII-8.—Comparison of specific rates k in the trimethylamine-ester reaction and acid strengths K. (Rate constants in terms of hours.)[100]

Linear Free-energy Relationships in Redox Reactions.—Rela- tionships involving the rate and equilibrium of the same series of reactions have been observed in the air oxidation of a series of leuco dyes,[98] in the reduction by a single reducing agent of a

[98] BARRON, *J. Biol. Chem.*, **97**, 287 (1932).

series of quinones,[99] and in the oxidation by a single oxidizing agent of a series of hydroquinones.[99] Since the standard free energy $\Delta G°$ of a redox reaction is related to its molar oxidation potential E by the equation

$$\Delta G° = -nFE \qquad (22)$$

the linear relationship between $\Delta G°$ and $-RT \ln k$ is equivalent to one between E and $\log k$. A plot of these quantities for the reaction of a series of quinones with the reductant dihydrolutidine dicarboxylic ester is shown in Fig. 7.

The Trimethylamine-ester Reaction.—In this reaction a linear relation is found[100] between the rate constants of the series of reactions

$$RCOOCH_3 + N(CH_3)_3 \rightarrow RCOO^- + N(CH_3)_4^+ \qquad (XIV)$$

and the ionization constants of the acids RCOOH, which are the equilibrium constants of a related series of reactions in which a proton is transferred from the acid to a base, instead of a methyl ion from the ester to a base. The data are plotted in Fig. 8 and satisfy the equation

$$\log k = -1.81 + 0.81 \log K \qquad (23)$$

with a median deviation of 0.07. In accordance with the close resemblance of the reactions the constants of which are compared, the relationship is satisfied with aliphatic as well as with aromatic esters and with ortho-substituted benzoic esters as well as with the meta and para derivatives.

[99] DIMROTH, *Z. angew. Chem.*, **46**, 571 (1933).
[100] HAMMETT and PFLUGER, *J. Am. Chem. Soc.*, **55**, 4079 (1933).

CHAPTER VIII

ENOLIZATION AND RELATED REACTIONS

The Base-induced Ketone Halogenation.—The way in which acids or bases affect the rate of a reaction is frequently a most useful symptom of the reaction mechanism. Thus the fact that bases in general, rather than hydroxyl ion alone, accelerate the iodination of acetone (page 226) furnishes further verification of the mechanism discussed in Chap. IV. If the rate-determining step in the halogenation, the racemization and the deuterium exchange under the influence of a base, is the proton transfer

$$\left[\begin{array}{c} \bar{O} \\ H_3C - C \\ CH_3 \end{array} \right]^- + B \rightarrow \left[\begin{array}{c} H_3C - C \div CH_2 \\ O \\ - \end{array} \right]^- + BH^+ \qquad (I)$$
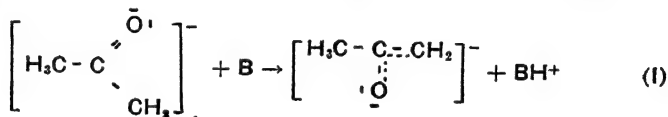
then any base, *i.e.*, any substance with a proton affinity, should be effective, more or less according to its basicity. The reaction should, therefore, exhibit the same dependence upon the nature and concentration of the bases present that appears in general base catalysis. With this final verification the mechanism reaches a remarkable degree of validity.

The only objection that has been suggested arises from the mistaken feeling that the simple proton transfer should be too rapid a reaction to be rate determining in the halogenation and the other reactions. Back of this feeling is the common knowledge that the ordinary neutralization and hydrolysis reactions of relatively strong acids and bases in aqueous solution are too fast for measurement and, perhaps, the long disproven dogma of the early theory of ionization that all ionic reactions are "instantaneous." The protolytic reaction of equation (I) is, however, the reaction of an extremely weak acid, the ketone, furthermore, an acid in which the proton is linked to carbon. The extension to this case of conclusions based on the behavior of much stronger acids in which the proton is attached to oxygen is a decidedly

dangerous extrapolation.   Indeed, reactions involving a proton linked to carbon of the type

$$\left[\begin{matrix} C_6H_5C_6H_4 \\ \diagdown \\ \diagup \\ (C_6H_5)_2 \end{matrix} C \,\colon \right]^- + (C_6H_5)_3CH \rightarrow \begin{matrix} C_6H_5C_6H_4 \\ \diagdown \\ \diagup \\ (C_6H_5)_2 \end{matrix} CH + [(C_6H_5)_3C\,\colon]^- \quad (II)$$
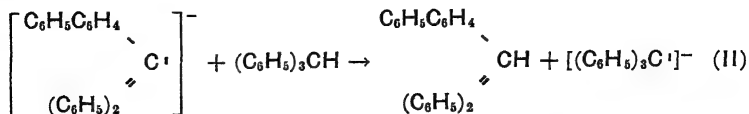
have been found[1] to have half times of hours or days at room temperature in ether solution.   It is an interesting fact that the proton transfer is much slower than the reaction of the carbanion with carbon dioxide

$$[(C_6H_5)_3C\,\colon]^- + CO_2 \rightarrow [(C_6H_5)_3CCO_2]^- \qquad (III)$$
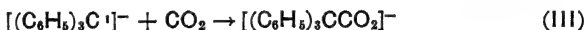
The high rate of the latter reaction makes possible the determination of the equilibrium of reactions of the type of (II) by the addition of carbon dioxide and the analysis of the resulting mixture of acids.   The results of this method are consistent with those of others.

On Catalysis and Acceleration.—Strictly speaking, the halogenation of a ketone is not *catalyzed* by bases and is not, therefore, subject to general basic catalysis, because the strict definition of a catalyst is a substance that accelerates a reaction without entering into the final reaction products.   But reaction (I) followed by

$$[H_3C\text{-}CO\text{-}CH_2]^- + Br_2 \rightarrow H_3C\text{-}CO\text{-}CH_2Br + Br^- \qquad (IV)$$
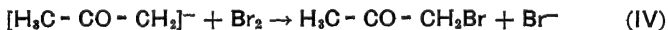
converts the catalyzing base to its conjugate acid.   In the older formulation of these reactions it was said that the halogenation produces hydrogen bromide, which neutralizes the catalyst as a secondary effect, but this puts the cart before the horse.

In the racemization, however, the base is regenerated, for the reaction depends upon the conversion of the ion formed from dextrorotatory ketone to levorotatory ketone.   The formation of the ion converts one mole of base to its conjugate acid, the reversion to ketone regenerates the base.   For the same reason the deuterium exchange is a catalysis in the strict definition.

The distinction between a catalysis and the kind of acceleration produced by bases in the halogenation reaction is obviously

[1] CONANT and WHELAND, *J. Am. Chem. Soc.*, **54**, 1212 (1932).   See also LEWIS and SEABORG, *ibid.*, **61**, 1886; 1894 (1939).

a formal one, lacking in any fundamental significance. A catalysis depends upon the accident that reactions subsequent to the rate-determining step regenerate one of the reactants involved in that step.

On Enolization and Ionization.—It has been customary to say that the rate-determining step of the halogenation is the *enolization* of the ketone. The terminology dates to the period when the ionization of a ketone was supposed to take place by way of an internal rearrangement of the nonacidic keto form to the acidic enol followed by the ionization of the enol. This mechanism is, however, absolutely inconsistent with the fact that the halogenation is accelerated by bases, unless one prefers the vague hypothesis that the mere presence of a base in the circumambient medium influences the rate of an internal shift of the proton over the simple and altogether satisfactory principle that the second-order kinetics implies a reaction of ketone with base as the rate-determining step.

The rate-determining step in the base-induced reactions is, therefore, the ionization of the ketone. In the light of the resonance picture it is no longer necessary to suppose that two forms of ion, a keto and an enol, must exist, the rearrangement of which, the one into the other, is part of the over-all reaction. Rather the incipient electron shift to form the electronic configuration present in the ion, which is a resonance hybrid of the keto and enol forms, must be taken as the source of a large part of the driving force of the ionization.

There is no reason to suppose that the formation of an electrically neutral enol form represents anything more than an unimportant by-path into which a portion of the reacting substance may transiently stray. The necessary and sufficient condition for the halogenation, the racemization, or the deuterium exchange is the formation of the ion.

Acid-catalyzed Enolizations.—The formation of the enol is, on the other hand, prerequisite for the same reactions under conditions of acid catalysis. The facts of the situation in this case are that the halogenation rate is independent of the concentration of halogen, except at very high acidities;[2] the rates of chlorination, bromination, and iodination are identical; there

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[2] ZUCKER and HAMMETT, *J. Am. Chem. Soc.*, **61**, 2791 (1939).

is a general acid catalysis;[3] the rates of halogenation and of racemization are the same within a few per cent.[4]

These phenomena can be accounted for by the reasonable hypothesis that the enolization takes place in two steps

$$R-C\overset{\bar{O}}{\underset{CH_3}{\diagdown}} + HA \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \left[R-C\overset{\bar{O}-H}{\underset{CH_3}{\diagdown}} \right]^+ + A^- \qquad (V)$$

$$\left[R-C\overset{\bar{O}H}{\underset{CH_3}{\diagdown}} \right]^+ + A^- \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} R-C\overset{\bar{O}H}{\underset{CH_2}{\diagdown}} + HA \qquad (VI)$$
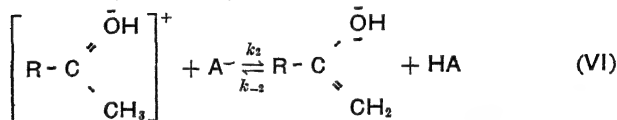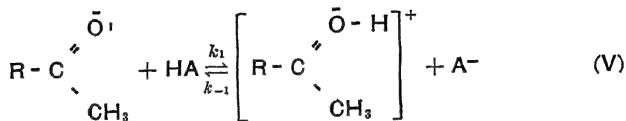
The first consists in the addition of a proton to the carbonyl oxygen. This can in itself lead neither to racemization nor to halogenation. It does not affect the asymmetric carbon in the former case; the ion may be expected to be less accessible to halogenation than the unreacted ketone. But the ionization must to a marked degree facilitate the removal of the proton from the α-carbon, both because of the positive charge on the ion and because of the altered electronic distribution which accompanies the ionization. The addition of the proton must displace the electronic system toward the proton and, therefore, away from the α-carbon; the resulting decrease in electron density in the neighborhood of the C—H link must be favorable to the separation of the proton. The essence of this acid catalysis and, no doubt, of many others is, therefore, that the addition of a proton at one point in the molecule greatly facilitates the removal of a proton from another point.

Once the enol is formed, it may react rapidly with halogen, a known reaction of isolable enols. Or in the absence of halogens it may revert to the ketone, and since the enol is symmetrical, this must lead to racemization if the ketone has an asymmetric α-carbon atom.

The Kinetics of the Acid-catalyzed Enolization.—As both enol and ion are unstable intermediates, the rate equations may be

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[3] (a) Ref. 88, Chap. VII. (b) Zucker and Hammett, *J. Am. Chem. Soc.*, **61**, 2785 (1939).

[4] Ingold and Wilson, *J. Chem. Soc.*, 773 (1934). Bartlett and Stauffer, *J. Am. Chem. Soc.*, **57**, 2580 (1935).

written down directly by substitution in the Christiansen equations (page 107). The result is relatively simple when only one acid and its conjugate base are involved, a situation often realizable in practice by suitable choice of experimental conditions. The steps of the bromination are those of equations (V), (VI),

$$
\text{R - C} \underset{CH_2}{\overset{\bar{O}\text{ - H}}{\diagup}} + {}^{!}\bar{B}r\text{ - }\bar{B}r{}^{!} \xrightarrow{k_3} \text{R - C} \overset{\bar{O}{}^{!}}{\diagdown}_{CH_2 \text{ - }\bar{B}r{}^{!}} + Br^- + H^+ \quad \text{(VII)}
$$
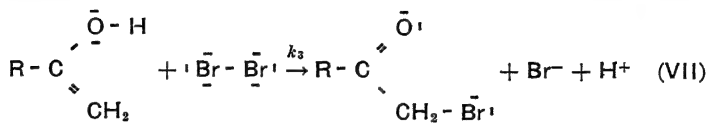
and (VII) with the specific rates indicated. Under the usual condition of irreversibility the quantity v_- vanishes and v_+ is given by

$$
\frac{1}{v_+} = \frac{1}{k_1[HA][K]} + \frac{k_{-1}[A^-]}{k_1[HA][K]k_2[A^-]} + \frac{k_{-1}[A^-]k_{-2}[HA]}{k_1[HA][K]k_2[A^-]k_3[Br_2]} \quad (1)
$$

To satisfy the experimental condition that the rate be independent of the concentration of bromine, the last term must be negligible compared with the others, and this is possible only if the ratio $k_{-2}[HA]/k_3[Br_2]$, by which it differs from the previous term, be very small. This means, of course, that the rate of bromination of the enol is very fast compared with that of its reversion to the ion. With the omission of the last term equation (1) reduces

$$
v = \frac{k_1 k_2 [HA][K]}{k_{-1} + k_2} \quad \text{and} \quad k_c = \frac{k_1 k_2}{k_{-1} + k_2} \quad (2)
$$

The mechanism leads, therefore, to the correct second-order dependence of rate upon the product of the concentrations of ketone and acid but makes the catalytic constant a function of the specific rates of two forward steps and one reverse step.

There are two limiting conditions of interest. If

$$
k_2 \gg k_{-1}, \quad \text{then} \quad k_c = k_1 \quad (3)
$$

equation (V) becomes the rate-determining step of the halogenation, and the catalytic constant reduces to the specific rate of this step. If, on the other hand,

$$
k_2 \ll k_{-1}, \quad \text{then} \quad k_c = \frac{k_1 k_2}{k_{-1}} = K_1 k_2 \quad (4)
$$

with K_1 the equilibrium constant of reaction (V). Reaction (VI) is rate determining, and the catalytic constant reduces to the

product of its specific rate by the equilibrium constant of reaction (V).   If neither limiting case applies, neither step can be taken as rate determining.

In the general case that more than one acid and base are involved, each step becomes the sum of a series of parallel and competing reactions, each of the w's of the Christiansen equations must be replaced by a summation, and instead of equation (2) the rate equation becomes

$$\frac{v}{[\mathrm{K}]} = \frac{\sum_{i}^{i} k_1^i [\mathrm{HA}^i] \sum_{j}^{j} k_2^i [\mathrm{A}^j]}{\sum_{j}^{j} k_2^i [\mathrm{A}^j] + \sum_{k}^{k} k_{-1}^k [\mathrm{A}^k]} \qquad (5)$$

This is a function of the concentrations of bases as well as of acids, but it reduces to a dependence upon the concentrations of the acids alone in either of the limiting cases that correspond to those just discussed in connection with equation (2).

If

$$\sum_{j}^{j} k_2^i [\mathrm{A}^j] \gg \sum_{k}^{k} k_{-1}^k [\mathrm{A}^k] \qquad (6)$$

the denominator of equation (5) reduces to its first term, which cancels with the second factor in the numerator, and the equation reduces immediately to

$$\frac{v}{[\mathrm{K}]} = \sum_{i}^{i} k_1^i [\mathrm{HA}^i] \qquad (7)$$

The first step is rate determining, and the rate reduces to the sum of terms that give the rate of reaction in this step of each of the acid catalysts.

The reduction is more complicated in the other extreme, *viz.,* when

$$\sum_{j}^{j} k_2^i [\mathrm{A}^j] \ll \sum_{k}^{k} k_{-1}^k [\mathrm{A}^k] \qquad (8)$$

Equation (5) then reduces to

$$\frac{v}{[\mathrm{K}]} = \frac{\sum_{i}^{i} k_1^i [\mathrm{HA}^i] \sum_{j}^{j} k_2^i [\mathrm{A}^j]}{\sum_{k}^{k} k_{-1}^k [\mathrm{A}^k]} \qquad (9)$$

Each $k_k^k{}_{-1}$ in the denominator may be replaced by the ratio k_1^k/K_1^k in which K_1^k is the equilibrium constant of reaction (V). If, furthermore, the system HA-A$^-$ has the usual mobility, the law of equilibrium gives

$$[A^k] = K_a^k \frac{[HA^k]}{[OH_3^+]} \tag{10}$$

Each ratio K_a/K_1 equals the equilibrium constant K of the reaction

$$K + OH_3^+ \rightleftharpoons I^+ + H_2O \tag{VIII}$$

and is independent of the catalyst. Hence equation (9) reduces to

$$\frac{v}{[K]} = \frac{\Sigma k_1[HA]\Sigma k_2[A]}{\{K/[OH_3^+]\}\,\Sigma k_1[HA]} \tag{11}$$

from which by cancellation and the use of equation (10)

$$\frac{v}{[K]} = \sum^i K_1^i k_2^i[HA^i] \tag{12}$$

Again the rate reduces to the sum of terms involving the concentrations of the acids only, but each catalytic constant is now, as in the simpler case [equation (4)], the product of the specific rate of the rate-determining second step by the equilibrium constant of the corresponding first step.[3b]

Aside from the case that only one acid and base are involved, when equation (2) applies, there is only one other condition that permits the rate to depend upon the concentrations of the acids only. This requires that for all the bases the ratio k_2/k_{-1} have the same value, which is not generally true but might be in a particular case.[3b]

The Kinetics of the Acid-catalyzed Racemization.—For a single catalyst the reaction steps are

$$dK + HA \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} dI^+ + A^- \tag{IX}$$

$$dI^+ + A^- \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} E + HA \tag{X}$$

$$E + HA \underset{k_2}{\overset{k_{-2}}{\rightleftharpoons}} lI^+ + A^- \tag{XI}$$

$$lI^+ + A^- \underset{k_1}{\overset{k_{-1}}{\rightleftharpoons}} lK + HA \tag{XII}$$
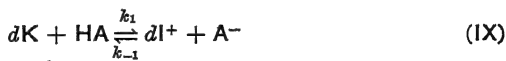
The symbols dK, dI$^+$, E, lI$^+$, and lK refer to dextrorotatory ketone and ion, enol, and levorotatory ion and ketone, respectively. The rate equations are easily written down in the Christiansen form and because of the equality of the specific rates for dextro- and levo-rotatory substances reduce to

$$v = \frac{1}{2}\frac{k_1 k_2 [\text{HA}]}{k_{-1} + k_2}\{[d\text{K}] - [l\text{K}]\} \tag{13}$$

and in terms of the rotation α to (page 109)

$$-\frac{1}{\alpha}\frac{d\alpha}{dt} = \frac{k_1 k_2 [\text{HA}]}{k_{-1} + k_2} \tag{14}$$

The specific rate of the racemization is, therefore, the same function of the rates of the various steps as that of the halogenation. If more than one catalyst is present, the right-hand side of equation (14) must be replaced by the fraction involving the summations that appears in equation (5).

The Question of the Third-order Reaction.—It is, in principle, possible that the enolization might go by way of a simultaneous attack of acid and base on the ketone, one adding a proton to the oxygen, the other removing one from carbon. Such a reaction requires the appearance in the equation for the rate of a term involving the product of the concentrations of acid and base. A similar term would also arise if the first step in the enolization were a reversible hydrogen bonding between ketone and acid, followed by a rate-determining reaction of the complex with the base.

$$R - C \overset{O}{\underset{CH_3}{\diagdown}} + HA_1 \rightleftharpoons R - C \overset{O\cdots H - A_1}{\underset{CH_3}{\diagdown}} \tag{XIII}$$

$$R - C \overset{O\cdots H - A_1}{\underset{CH_3}{\diagdown}} + A_2^- \rightleftharpoons R - C \overset{O - H}{\underset{CH_2}{\diagdown}} + HA_2 + A_1^- \tag{XIV}$$
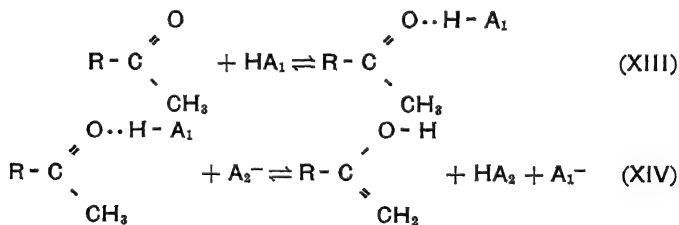
The available data[5] on the iodination of acetone in acetate buffers satisfy the equation

$$k = 1.30 \times 10^{-6}[\text{HA}] + 3.3 \times 10^{-6}[\text{A}^-] + 3.5 \times 10^{-6}[\text{HA}][\text{A}^-] + 0.006 \times 10^{-6} \tag{15}$$

[5] DAWSON and SPIVEY, *J. Chem. Soc.*, 2180 (1930).

The term involving the product is probably necessary, but this is not unambiguously demonstrated because the proof of its presence involves small differences between large quantities. Furthermore, an equation of this form might be approximated by equation (5) without involving the termolecular or hydrogen bonding alternatives.

It seems clear in any case that the reaction cannot go exclusively or even predominantly by the termolecular mechanism of a simultaneous attack of acid and base.[6] If this were the case, the first term on the right must involve a simultaneous attack on the acetone by the base water and by the acetic acid, the second term an attack by the acid water and the base acetate ion, and the fourth an attack by two molecules of water one acting as base the other as acid.   The figures show that in case the base is water, the reaction goes 220 times faster (1.30/0.006) when the acid is acetic acid than when it is water.   When the base is acetate ion, the rate of reaction with the acetic acid ought to be faster than that with the acid water in about the same proportion; consequently, the termolecular hypothesis predicts a value of $220 \times 3.3 \times 10^{-6} = 700 \times 10^{-6}$ instead of the observed value of 3.5×10^{-6} for the coefficient of the third term of equation (15).

The Problem of the Rate-determining Step: Evidence from the Base Strengths of Ketones.—If the enolization goes in two steps, one must be faster than the other and, therefore, rate determining.   There is, incidentally, an apparent but not a real paradox in the fact that the rate-determining step of an acid-catalyzed reaction may be a process in which a base is converted to an acid [reaction (VI)].   The situation arises because the rate-determining step is preceded by an equilibrium in which an acid is converted to a base.

Evidence that reaction (VI) rather than (V) is rate determining may be derived from the following considerations.   Reaction (V) is simply a proton transfer to a base, the ketone, from the catalyzing acid.   In the base-catalyzed halogenation or racemization the rate-determining step is a similar proton transfer [reaction (I)].   But it is purely an accident that the proton transfer is followed by other reactions which make the base the

[6] PEDERSEN, Dis., Copenhagen, 1932; *J. Phys. Chem.*, **38**, 581 (1934).

substrate in one case, the catalyst in the other. Consequently, the applicability of the Brønsted law in both cases demonstrates that in any proton transfer a linear free-energy relationship must apply between the rates of reaction of a series of bases and the strengths of the bases. Specifically, therefore, the rates of reaction of a series of ketones with the same catalyst in reaction (V) must exhibit the linear free-energy relation to their base strengths.[6,7] If reaction (V) is rate determining, the same relation must appear between enolization rate and base strength.

If, however, reaction (VI) is rate determining, the catalytic constant is the product of the equilibrium constant of reaction (V), which is a direct measure of the proton affinity of the carbonyl oxygen, by the specific rate k_2 of an entirely different process, the removal of a proton from the α-carbon. If the structures of a series of ketones differ by substitutions in the neighborhood of the reacting group, as in the series $C_6H_5COCH_3$, $C_6H_5COCH_2CH_3$, and $C_6H_5COCH(CH_3)_2$, no linear free-energy relation can be expected to apply between the base strength and the value of k_2; hence none will apply between base strength and catalytic constant (page 224).

When the base strengths of this series of ketones, together with some others, are measured by methods to be described (page 271) and plotted logarithmically against the first-order constants k for the halogenation in 1.388M perchloric acid, the complete lack of correlation shown in Fig. 1 is obtained.[3b] The result argues strongly against reaction (V) as the rate-determining step.

Evidence from the Isotopic Oxygen Exchange.[8]—When acetone is mixed with water containing an abnormal proportion of the oxygen isotope of atomic weight 18, no measurable interchange of oxygen between acetone and water occurs unless acid or base catalysts are present. There is a general acid catalysis, a catalysis by hydroxyl ion, but apparently no general basic catalysis. In an equimolar mixture of acetone and water at 100° the catalytic constants are 1.94 for oxonium ion and 0.00114 for salicylic acid, and the rate shows the same kind of dependence

[7] HAMMETT and PFLUGER, *J. Am. Chem. Soc.*, **55**, 4079 (1933). BELL, *Proc. Roy. Soc.* (London), **A154**, 414 (1936).

[8] COHN and UREY, *J. Am. Chem. Soc.*, **60**, 679 (1938).

upon the concentration of a salicylate buffer as is found in the orthoacetate hydrolysis. The probable mechanism[8] of the exchange consists in the proton transfer of reaction (V), followed by the addition of a molecule of H_2O^{18} to form (A), the reaction of this

$$
\begin{bmatrix}
CH_3 & O^{16}-H \\
& C & H \\
CH_3 & O^{18} \\
& & H
\end{bmatrix}^+
\qquad
\begin{matrix}
CH_3 & O^{16}-H \\
& C \\
CH_3 & O^{18}-H
\end{matrix}
$$

(A) (B)
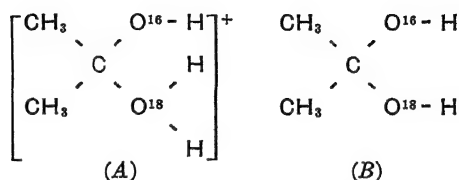
with a base to form the ketone hydrate (B), and the reversion of this to a ketone molecule which is as likely to contain O^{18} as O^{16}
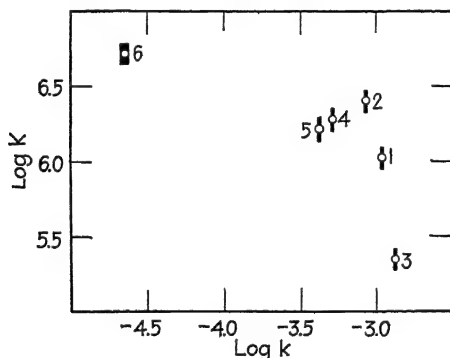
Fig. VIII-1.—Comparison of base strengths of ketones K with specific rates of halogenation k.[3b] 1, acetophenone; 2, p-bromacetophenone; 3, p-methylacetophenone; 4, propiophenone; 5, n-butyrophenone; 6, i-butyrophenone.

Whichever of these steps is rate determining, the over-all rate of the exchange cannot be greater than the rate of its first step reaction (V); it may be smaller if the first step is reversible and followed by a later rate-determining step. Consequently, if the oxygen exchange is faster than the halogenation, reaction (V) must also be faster than the halogenation and cannot be its rate-determining step. No exact comparison under identical conditions has been made, but a reasonable interpolation from the rates of halogenation in pure acetone and in dilute solutions of acetone in water indicates that the enolization rate is, in fact, several orders of magnitude slower than the oxygen exchange

and, consequently, that reaction (V) is not rate determining in the former reaction.

Kinetics of Enolization in Deuterium Oxide.—The first evidence historically[9] on the question of the rate-determining step, but hardly the surest demonstration of its correct answer, arises from the comparison of reaction rates in D_2O and H_2O. The acid-catalyzed enolization of acetone is 2.10 times faster in the deuterium solvent.[10] It is, however, to be expected that the deuteron transfer

$$\begin{array}{c} CH_3 \\ \diagdown \\ \diagup \\ CH_3 \end{array} C = O + DA \rightleftharpoons \left[\begin{array}{c} CH_3 \\ \diagdown \\ \diagup \\ CH_3 \end{array} C = OD \right]^+ + A^- \qquad (XV)$$
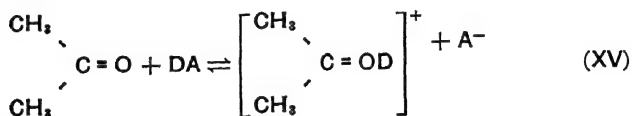
should be slower than the proton transfer of reaction (V). This effect is predicted from theory[11] on the basis of reasonable assumptions about the zero-point energies of the proton and deuteron vibrations in the reacting molecules and in the transition states, and the reactions of nitromethane and of an enolizable ketone with bases show a rate in D_2O slower by a factor of 3 to 7.[12] If reaction (VI) is rate determining in the enolization, the specific rate is the product of the rate constant k_2 of a reaction which still involves a proton transfer even in deuterium water by an equilibrium constant, which for all that theory or experience prescribes may either increase or decrease on transfer from the protium to the deuterium system.

The weight of this argument is weakened by the discovery[13] in the case of the orthocarbonate hydrolysis, which shows an unmistakable general acid catalysis, that the catalytic constant for oxonium ion is increased, although that for acetic acid is decreased by the transfer to D_2O.

Reaction Products in the Halogenation.[14]—The first isolable product in the base-catalyzed halogenation of acetone is the

[9] BONHOEFFER, *Trans. Faraday Soc.*, **34**, 252 (1938).

[10] REITZ, *Z. physik. Chem.*, A179, 119 (1937).

[11] WYNNE-JONES, *Chem. Rev.*, 17, 115 (1935).

[12] REITZ, *Z. physik. Chem.*, A176, 363 (1936). WILSON, *J. Chem. Soc.*, 1550 (1936).

[13] WYNNE-JONES, *Trans. Faraday Soc.*, **34**, 245 (1938).

[14] BARTLETT, *J. Am. Chem. Soc.*, **56**, 967 (1934).

unsymmetrical trihalogen derivative, *e.g.*, CH_3COCBr_3.   This is because the bromine in CH_3COCH_2Br is strongly electron attractive and facilitates the removal of the adjacent proton. Consequently, the specific rate of ionization [reaction (I)] and hence of halogenation of bromacetone is greater than that of acetone, and that of dibromacetone is still larger.   The mono and dibrom compounds react relatively rapidly, therefore, as soon as they are formed and never attain a sufficient concentration to permit isolation.   In the acid-catalyzed reaction, bromine substitution decreases the equilibrium constant K_1 whereas it increases the rate constant k_2.   The net effect upon the enolization rate is not predictable but turns out experimentally to be a decrease.   The mono and dibrom compounds are, therefore, isolable intermediates.

General Acid and Base Reactions as Criteria of Mechanism.— When a reaction is of the general acid or base type, catalytic or otherwise, its rate-determining step is most probably a proton transfer of the type involved in the ketone halogenation and related reactions.   The only apparent alternative is that of a reversible hydrogen bonding between substrate and acid followed by a nonprotolytic reaction of the complex thus formed. This leads, however, to no satisfactory picture of the reaction process in a base catalysis and to one of limited applicability in the case of an acid catalysis.   The conclusions that may be drawn from the existence of a specific oxonium or hydroxyl-ion catalysis are less definite.   One alternative is that of a mobile and reversible proton transfer followed by a rate-determining nonprotolytic reaction.   Thus the base-catalyzed ketone halogenation may become first order in halogen (page 106) if the specific rate of reaction of ion with halogen ($k_2[Br_2]$) is slow compared with that of its reversion to ketone ($k_{-1}[BH^+]$).   This makes the second term in equation (41), Chap. IV, much larger than the first and reduces the rate equation to

$$v = \frac{k_1 k_2}{k_{-1}} \frac{[K][B][Br_2]}{[BH^+]} = K_1 k_2 \frac{[K][B][Br_2]}{[BH^+]} \tag{16}$$

Because of the presence of the ratio $[B]/[BH^+]$ in this equation, a simultaneous and proportionate increase in concentrations of

the base and its conjugate acid do not alter the rate. Since, furthermore,

$$\frac{[B]}{[BH^+][OH^-]} = \frac{1}{K_i} \tag{17}$$

and

$$\frac{K_1}{K_i} = K \tag{18}$$

where K is the equilibrium constant of the reaction

$$K + OH^- \rightleftharpoons I^- + H_2O \tag{XVI}$$

equation (16) may be put in the form

$$v = Kk_2[OH^-][K][Br_2] \tag{19}$$

which is characteristic for a specific hydroxyl-ion reaction.

Another alternative is a rate-determining proton transfer with a catalytic constant for oxonium ion or hydroxyl ion so large that catalysis by other acids or bases is not detectable. This is most likely to be the case when the slope x of the Brønsted equation is large.[15] The greater the value of the slope, the more rapidly will the catalytic constant increase with increasing acid or base strength of the catalyst. Since oxonium ion is the strongest acid and hydroxyl ion the strongest base obtainable in appreciable concentration in aqueous solution, their catalytic constants will probably be especially large when x is large. This will be true even though their representative points deviate considerably (as they often do) from the relationship established from the study of other catalysts (page 225).

Finally a base-catalyzed reaction in water solution may depend upon the addition of hydroxyl ion to a carbonyl group. This is probably the case in the hydroxyl-ion catalyzed oxygen exchange in acetone, the probable intermediates of which are (C) and (D) with the first step rate determining.[8]

(C) (D)
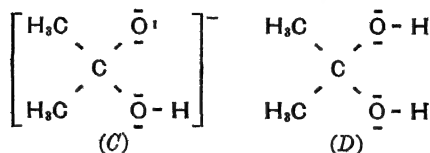
[15] Brønsted and Wynne-Jones, *Trans. Faraday Soc.*, **25**, 59 (1929).

If the problem of the relative rates of proton and deuteron transfer were on a surer basis (page 240), it would assist materially in distinguishing these alternatives. Another possibility (page 276) involves the effect of high acidities upon the rate, but this also requires further substantiation.

The Structural Requirements for an Acidic Proton.—Enolization, racemization, halogenation, and deuterium exchange all require the removal of a proton from combination with carbon by the attack of a base; they involve a nucleophilic displacement on hydrogen. None of them are known to occur unless there is unsaturation or a high concentration of positive charge on an adjacent carbon atom. Thus exchange of deuterium for hydrogen under the influence of bases occurs on the α-carbon atom of ketones, acids, esters, nitriles, and similar substances and in such highly unsaturated hydrocarbons as cyclopentadiene, indene, fluorene, and acetylene.[9] The rate of exchange in the ion (E)

$$
\left[\begin{array}{c}
C_6H_5 \quad D \\
\diagdown \quad \diagup \\
C \quad \bar{O} \\
\diagup \quad \diagdown \\
CH_3C_6H_5 \quad C \\
\diagdown \\
\bar{O}
\end{array}\right]^- \quad
\begin{array}{c}
H - C \text{——} \bar{S} \\
\| \quad \| \\
H_3C - C \quad C - H \\
\diagdown \quad \diagup \\
N \\
\underline{\ }
\end{array} \quad
\left[\begin{array}{c}
H \quad O \\
| \quad \| \\
H_2C - C - C - OC_2H_5 \\
| \\
CH_3 - N - CH_3 \\
| \\
CH_3
\end{array}\right]^+
$$

$$(E) \qquad\qquad (F) \qquad\qquad (G)$$
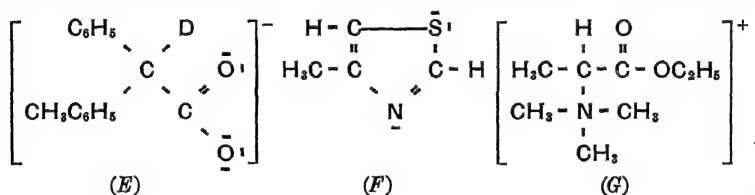
is identical with its rate of racemization.[16] Deuterium exchange also appears under the action of caustic alkali in o- and p-nitrotoluene and in quinaldine.[17] It is possible in these cases because of the powerfully electron-attractive nature of the nitro group and of the well-demonstrated similar effect of the ring nitrogen in pyridine derivatives. The exchange also appears in the methyl derivatives of other heterocycles such as (F).[18] The effect of the nitro group may even lend acidity to the ring hydrogens in benzene derivatives, for trinitrobenzene exchanges.[17] The expected unfavorable effect on acidity of a negative charge in the molecule appears in the fact that esters and amides are more rapidly racemized by bases than the corresponding car-

---

[16] Ives and Willis, *J. Chem. Soc.*, 1455 (1938).

[17] Kharasch, Brown, and McNab, *J. Org. Chem.*, **2**, 36 (1937).

[18] Erlenmeyer and Weber, *Helv. Chim. Acta*, **21**, 863 (1938). Erlenmeyer, Weber, and Wiessmer, *ibid.*, **21**, 1017 (1938).

boxylate ions,[19] the expected favorable effect of a positive charge in the easy racemization of (G).[20]

When two unsaturated or otherwise strongly electron-attracting groups are attached to a single carbon atom, protons attached to that carbon become especially acidic. With unsaturated groups this arises from the double resonance that exists in the conjugate base as in the case of acetacetic ester (H)

(H)
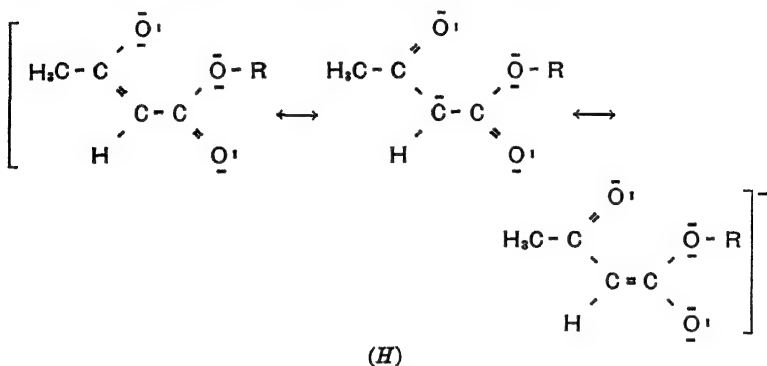
Other familiar examples are malonic ester, acetylacetone, and cyanacetic ester; the relatively easy D exchange[21] of phenylacetate and vinylacetate ions shows that the effect exists in them also. In the very readily[22] brominated and racemized sulfone CH_3—SO_2—$CHCH_3$—CO_2H there should be no resonance involving structures with a sulfur-carbon double bond, but the large positive charge on the sulfur kernel has the same electron-attracting effect that the resonance would produce.

Acetacetic ester and nitromethane are acids of strength comparable to that of phenol,[23] the ionization constants at 25° being for acetacetic ester 2.0×10^{-11}, for nitromethane 2.6×10^{-11}, for phenol 1.0×10^{-10}. The so-called pseudo-acids in which the proton is attached to carbon do not, therefore, differ widely in

[19] (a) BICKEL, *J. Am. Chem. Soc.*, **60**, 927 (1938). (b) BOVARNICK and CLARKE, *ibid.*, **60**, 2426 (1938).

[20] BIILMANN and BERG, *Bull. soc. chim.*, **1**, 1645; 1653 (1934).

[21] IVES and RYDON, *J. Chem. Soc.*, 1735 (1935). IVES, *ibid.*, 81; 91 (1938).

[22] MELLANDER, *Arkiv. Kemi, Mineral. Geol.*, **12A**, No. 1; No. 16 (1936).

[23] (a) GOLDSCHMIDT and OSLAN, *Ber.*, **33**, 1146 (1900). (b) JUNELL, Dis., Upsala, 1935.

strength from those in which the proton is on oxygen; they do differ enormously in rate of reaction, that of phenol being practically instantaneous.

Deuterium exchange may be induced by acids as well as by bases and is favored by electron-repelling substituents instead of by electron-attracting ones.[24] The rate increases in the order C_6H_6, $C_6H_5OCH_3$, $C_6H_5N(CH_3)_2$, $C_6H_5O^-$.

Enolization of Acetacetic Ester Derivatives.—The rate of bromination of ethyl acetoacetate is independent of the bromine concentration and shows a general base catalysis but no appreciable acid catalysis.[25] There is a small amount of instantaneous bromination owing to the enol present in equilibrium with the keto form, and the specific rate of the reaction of monobromacetacetic ester is about ten times that of acetacetic ester. For this reason the monobrom derivative is neither an end product nor an unstable intermediate, and the kinetics are relatively complicated.

The rate of conversion of the keto form of the menthyl ester of α-phenylacetacetic acid to the enol form catalyzed by piperidine in hexane solution has been determined by making use of the fact that the enol reacts instantaneously with halogen. The rate of the mutarotation, which involves the inversion of the configuration of the α-carbon atom of the keto form as well as the conversion of keto to enol, has also been measured optically.[26] If the inversion went only by the reversible conversion of keto to enol, the reaction system would be

$$d\mathsf{K} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathsf{E} \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} l\mathsf{K} \qquad (XVII)$$

The enol E is not an unstable intermediate, and the method of Rakowski (page 105) must be applied to the integration of the rate equations. The result is unmanageable unless the reasonable assumptions (reasonable because the center of asymmetry in the menthyl group is so far from the reacting one) are made that $k_2 = k_{-1}$ and $k_1 = k_{-2}$. Furthermore, it is known that the

[24] INGOLD, RAISIN, and WILSON, *J. Chem. Soc.*, 1637 (1936). BEST and WILSON, *ibid.*, 28 (1938).

[25] PEDERSEN, *J. Phys. Chem.*, **38**, 601; 999 (1934).

[26] KIMBALL, *J. Am. Chem. Soc.*, **58**, 1963 (1936).

percentage of enol form present at equilibrium is 71, from which the ratio $k_1/k_{-1} = k_{-2}/k_2 = 4.9$. It can then be shown that the specific rate of the enolization $\dfrac{d \ln ([E] - [E]_e)}{dt}$ (where $[E]_e$ is the equilibrium concentration of the enol form) is equal to $k_1 + 2k_{-1}$, whereas the specific rate of the mutarotation $\dfrac{d \ln (\alpha - \alpha_e)}{dt}$ should be some 25 per cent lower.

Actually, the mutarotation runs about three times as fast as the enolization, and it is necessary to admit the presence of some racemizable intermediate between keto and enol forms. The kinetic system is presumably

$$d\mathrm{K} + \mathrm{B} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \underbrace{\mathrm{I}^- + \mathrm{BH}^+}_{k_3 \downarrow \uparrow k_{-3}} \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} l\mathrm{K} + \mathrm{B} \qquad \text{(XVIII)}$$
$$\mathrm{E} + \mathrm{B}$$
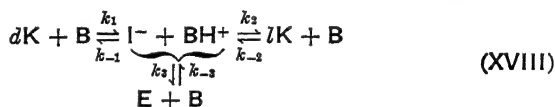
If $k_2 = k_{-1}$ and $k_1 = k_{-2}$, the threefold ratio of rates of mutarotation and enolization requires that $k_{-1} + k_2 = 2k_3$, *i.e.*, that about twice as many ions revert to the equimolar mixture of $d\mathrm{K}$ and $l\mathrm{K}$ as go on to enol.

The result is somewhat surprising; for one expects the addition of the proton to oxygen, which forms the enol, to be more mobile than the addition to carbon, which forms the keto. This is, however, mostly because the classical method of preparing the enol form is the acidification at low temperatures of the sodium salt suspended in hexane.[27] At the temperatures in question the equilibrium is so largely in favor of the enol form that the result may have nothing to do with the relative rates of formation of keto and enol forms, and in any case it predicts nothing about conditions at room temperature. In the entirely analogous addition of CH_3^+ by treatment of the sodium acetacetic ester with methyl iodide, the product is predominantly the keto form of α-methylacetacetic ester, which results from the addition to carbon.

Olefin Bond Migrations.—Another case in which the first step of a base-catalyzed prototropic isomerization is mobile and

[27] KNORR, ROTHE, and AVERBECK, *Ber.*, **44**, 1138 (1911).

reversible is found in the reaction[28]

$$
\begin{array}{c}
\text{CH}_2\text{-CH}_2 \\
\diagup \qquad \diagdown \\
\text{CH}_2 \qquad\qquad \text{C-CH}_2\text{-CN} \rightarrow \\
\diagdown \qquad \diagup \\
\text{CH}_2\text{-CH}
\end{array}
\qquad
\begin{array}{c}
\text{CH}_2\text{-CH}_2 \\
\diagup \qquad \diagdown \\
\text{CH}_2 \qquad\qquad \text{C = CH - CN} \\
\diagdown \qquad \diagup \\
\text{CH}_2\text{-CH}_2
\end{array}
$$
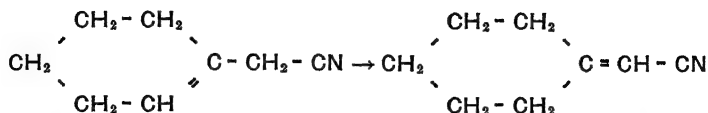
which proceeds largely to completion in the direction shown, resonance with the cyanide group being no doubt responsible for the stability of the α,β unsaturated form. The β,γ compound has been shown to exchange two protons for deuterons too rapidly for measurement under conditions (0.1N sodium ethoxide in ethanol at 25°) for which the half time of the isomerization is 7 hr. As both reactions undoubtedly proceed by way of the removal of an α-hydrogen, the rate at which the ion reverts to the less stable β,γ form must be much greater than that at which it is converted to the more stable α,β form. There is no inconsistency; the equilibrium condition requires merely that $k_1 k_2 > k_{-1} k_{-2}$, the rate condition that $k_{-1} > k_2$.

The Methyleneazomethine Rearrangement.—Reactions of the type

$$
\begin{array}{c}
p\text{-C}_6\text{H}_5\text{-C}_6\text{H}_4 \\
\diagdown \\
\qquad \text{CH - N = C} \\
\diagup \\
\text{C}_6\text{H}_5
\end{array}
\begin{array}{c}
\text{C}_6\text{H}_5 \\
\diagup \\
\\
\diagdown \\
\text{H}
\end{array}
\underset{k_r}{\overset{k_f}{\rightleftharpoons}}
\begin{array}{c}
p\text{-C}_6\text{H}_5\text{-C}_6\text{H}_4 \\
\diagdown \\
\qquad \text{C = N - C - H} \\
\diagup \\
\text{C}_6\text{H}_5
\end{array}
\begin{array}{c}
\text{C}_6\text{H}_5 \\
\diagup \\
\\
\diagdown \\
\text{H}
\end{array}
\qquad \text{(XIX)}
$$

$$(I) \qquad\qquad\qquad\qquad (J)$$
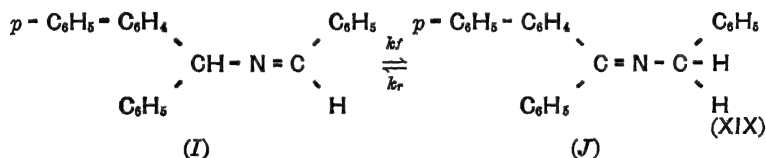
are subject to base catalysis and come to an equilibrium in which measurable amounts of the two substances are present. The sum $k_f + k_r$ may be obtained from the rate expression for a reversible reaction (page 102)

$$\ln \frac{x_e}{x_e - x} = (k_f + k_r)t \tag{20}$$

and, since the determination of the state of equilibrium permits the calculation of the ratio, k_f/k_r, k_f is also accessible. The substance (I) may be obtained optically active, (J) is necessarily inactive. If there is no racemizable intermediate, the specific

[28] INGOLD, DE SALAS, and WILSON, *J. Chem. Soc.*, 1328 (1936).

rate of racemization $-\dfrac{d \ln \alpha}{dt}$ is simply k_f, for the reversal of the reaction can regenerate only inactive (I). Actually,[29] the value of k_f determined from the rearrangement in $0.1N$ sodium ethoxide in ethanol at $25°$ is 3.55×10^{-6}, that from the racemization is 3.39×10^{-6}. The same kind of agreement has also been obtained[29,30], by a somewhat more complicated method, for the reaction in the same way of the substances (K) and (L)

$$\begin{array}{ccccc}
C_6H_5 & & C_6H_4Cl & C_6H_5 & & C_6H_5 \\
& CH - N = C & & & CH - N = C & \\
CH_3 & & C_6H_5 & CH_3 & & C_6H_5 \\
& (K) & & & (L) &
\end{array}$$

There are three possible interpretations of this phenomenon:

1. The rearrangement goes by the simultaneous addition and removal of a proton[30]

$$C_2H_5O^- + \begin{array}{c} R \\ CH - N = C \\ R \end{array} \begin{array}{c} R \\ \\ R \end{array} + HOC_2H_5 \rightleftharpoons C_2H_5OH +$$

$$\begin{array}{c} R \\ C = N - CH \\ R \end{array} \begin{array}{c} R \\ \\ R \end{array} + OC_2H_5^- \quad (XX)$$

with no intermediate. The contrast with the keto-enol change in which the ionic intermediate is highly probable may be explained on the basis that the ion in this case $[R_2C {=\!=\!=} N {=\!=\!=} CR_2]^-$ is much more basic than the one $[R_2C {=\!=\!=} C {=\!=\!=} O]^-$ involved in the other. The activation energy required for the removal of the proton from the nitrogen compound is, therefore, so large that the termolecular mechanism becomes easier than the two-step one.

2. There is an ionic intermediate, but it retains its configuration, and the reversal of the ionization yields the reacting substance with unchanged rotation. This involves the unsettled question of the optical stability of carbanions.

3. An ionic intermediate is formed, but practically every ion formed from (I) is converted to (J), *i.e.*, the ionization is prac-

[29] Hsü, Ingold, and Wilson, *J. Chem. Soc.*, 1778 (1935).
[30] Ingold and Wilson, *J. Chem. Soc.*, 93 (1934).

tically irreversible. It is extremely unlikely that this can be true of the three very differently constituted substances (I), (K), and (L).

The more probable interpretations 1 and 2 are both subject to one difficulty in the fact that the reaction product obtained by the rearrangement of (K) is at least 90 per cent racemic,[31] although it contains an asymmetric carbon atom. Either the termolecular process or a two-step one involving an asymmetric ion might be expected to produce active product by a sort of asymmetric synthesis. The interpretation of the reaction is also complicated by the fact that the deuterium exchange is appreciably more rapid than the rearrangement.[32]

Aliphatic Nitro Compounds.—These have properties very similar to those of acetacetic ester. Both true nitro (M) and aci (N) forms can be isolated in certain cases.[33] When a solution of

$$
\text{H}_3\text{C}-\overset{\scriptstyle O}{\underset{\scriptstyle O}{N}} \qquad \overset{\text{H}}{\underset{\text{H}}{\Large\rangle}}\text{C}=\text{N}\overset{\text{O}-\text{H}}{\underset{\text{O}}{\Large\langle}} \qquad \text{or} \qquad \text{H}-\overset{\text{H}}{\underset{\text{O}}{\text{C}}}-\text{N}-\text{O}-\text{H}
$$

$$(M) \qquad\qquad\qquad (N)$$
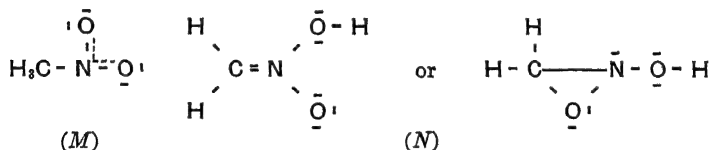
(M) or one of its derivatives is treated with sodium hydroxide, the conductivity decreases at a measurable rate[34] as a result of the reaction

$$\text{CH}_3\text{NO}_2 + \text{OH}^- \rightleftharpoons \text{CH}_2\text{NO}_2^- + \text{H}_2\text{O} \qquad\qquad \text{(XXI)}$$
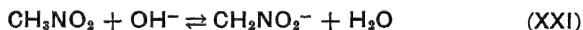
the anion of the nitro compound having a lower mobility than the hydroxyl ion. Conversely, the addition of acid to a solution of the sodium salt is followed by a measurably slow decrease in conductivity by virtue of the reaction

$$\text{CH}_2\text{NO}_2^- + \text{OH}_3^+ \rightleftharpoons \text{CH}_3\text{NO}_2 + \text{H}_2\text{O} \qquad\qquad \text{(XXII)}$$

The conductivity changes furnish the most accurate[35] method of following the rates of the reactions; they may also be measured

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[31] INGOLD and WILSON, *J. Chem. Soc.*, 1493 (1933).

[32] DE SALAS and WILSON, *J. Chem. Soc.*, 319 (1938).

[33] HANTZSCH and SCHULTZE, *Ber.*, **29**, 699 (1896).

[34] HOLLEMAN, *Rec. trav. chim.*, **14**, 121 (1895).

[35] MARON and LA MER, *J. Am. Chem. Soc.*, **60**, 2588 (1938); **61**, 692 (1939).

by using the instantaneous reaction of the ion with bromine.[23b,36] The conversion of nitromethane to the ion may result from the action of other bases than hydroxyl ion and obeys the same kinetic laws as a general base-catalyzed reaction. The reverse reaction is of the general acid type but is complicated by the rapid and reversible conversion of some of the ion to the aci form (*N*). From the study of these complications it is possible to determine the equilibrium constant for the ionization of the aci form $[\text{ion}^-][\text{OH}_3^+]/[\text{aci}] = 0.0006$ as well as the much smaller ionization constant for the nitro form $[\text{ion}^-][\text{OH}_3^+]/[\text{nitro}] = 2.6 \times 10^{-11}$. The corresponding values for nitroethane are 7×10^{-5} and 2.7×10^{-9}.

[36] PEDERSEN, *Kgl. Danske Videnskab. Selskab, Math.-fys. Medd.*, **12**, No. 1 (1932).

CHAPTER IX

THE QUANTITATIVE STUDY OF ACIDS AND BASES

The Determination of Oxonium-ion Concentration.—The fundamental reference point from which all measurements of oxonium-ion concentration in aqueous solution must start is the solution of a strong acid, such as HCl, in which the reaction

$$HCl + H_2O \rightleftharpoons OH_3^+ + Cl^- \tag{1}$$
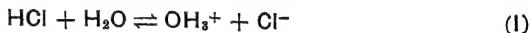
goes practically to completion and the oxonium-ion concentration is practically equal to the stoichiometric concentration of the acid. The vitally important proof that an acid is strong may be obtained from one or more of the following considerations. If the variation of conductivity or activity of an acid in dilute solutions is that predicted by the theoretical expressions of Debye and Hückel and of Onsager,[1] which take account of the electrical forces between the ions, one may assume that the ionization is complete. A strong electrolyte has a molar conductivity that varies with the square root of the concentration in dilute solutions; an electrolyte the ionization of which is incomplete has one that varies with the first power of the concentration. Or if the electrometric titration curve obtained when an acid is neutralized agrees with the theoretical one for a strong acid, the same conclusion of complete ionization may be drawn.[2] Or one may use the principle, so important in the development of the ionic theory, that a group of electrolytes which show a pronounced and exact additivity of properties must be composed of strong electrolytes.[3] Finally, indicator properties might be used. Picrate ion is intensely yellow, molecular picric acid is known from its behavior in concentrated

[1] Debye and Hückel, *Physik. Z.*, **24**, 185; 305 (1923). Onsager, *ibid.*, **27**, 388 (1926); **28**, 277 (1927).

[2] (a) Hall and Werner, *J. Am. Chem. Soc.*, **50**, 2367 (1928). (b) Hammett and Dietz, *ibid.*, **52**, 4795 (1930).

[3] Hammett, "Solutions of Electrolytes," 2d ed., New York, 1936, Chap. I.

acid solutions to be colorless.   Hence a colorimetric determination of the concentration of picrate ion in a dilute aqueous solution of the acid might be used to demonstrate that its ionization is nearly complete.

Given the point of reference, there are numerous ways in which oxonium-ion concentrations may be determined.   If one knows the equivalent conductivity of a strong acid, of its sodium salt, and of the sodium salt of a weak acid, one may calculate the conductivity the weak acid would have if it were completely ionized (called the conductivity at infinite dilution) and, by comparison with the actual conductivity of a solution of the weak acid, determine its degree of ionization α and the oxonium-ion concentration of the solution.   By application of the law of equilibrium

$$K = \frac{[A^-][OH_3^+]}{[HA]} = \frac{c\alpha^2}{1 - \alpha} \tag{1}$$

in which c is the stoichiometric concentration of the acid, the ionization constant K may be calculated and, from this, the oxonium-ion concentration of any solution of the acid alone or in a buffer mixture with one of its salts.   The result is precise only to the extent that concentrations may be substituted for activities, *i.e.*, in very dilute solutions, or that known activity coefficients have been used to correct equation (1).

The Indicator Method.—Relative values of the oxonium-ion concentration may be obtained with an indicator (page 91) by use of the equilibrium equation

$$\frac{[OH_3^+][B]}{[A]} = K_i = \frac{Kf_A}{(f_B f_{OH_3^+})} \tag{2}$$

in which A is the indicator acid, B its conjugate base.   If the ratio [A]/[B] is determined colorimetrically in a solution of known oxonium-ion concentration, the indicator constant K_i is immediately known.   From this the oxonium-ion concentration of any solution may be determined by a colorimetric measurement provided that the activity coefficient expression has the same value as in the previous measurement (*e.g.*, if the salt effect has been suppressed by the method of page 94) or if its variation may be neglected or calculated.   Both in the determination of

the indicator constant and in the measurement of the oxonium-ion concentration it is necessary that the acidity be neither so high nor so low that the indicator ratio [A]/[B] cannot be distinguished experimentally from infinity or zero. Each indicator has, therefore, a useful range of acidity, the center of which lies at an oxonium-ion concentration equal to the indicator constant.

The Electrometric Method.—A concentration cell of the type

$$\text{Pt, } H_2 \text{, Soln. 1, sat. KCl, Soln. 2, } H_2 \text{, Pt}$$
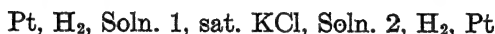
or of equivalent types involving quinhydrone or glass electrodes may be employed for the measurement of relative values of oxonium-ion concentration; for the potential of the cell is approximately determined by the equation

$$E = \frac{RT}{F} \ln \frac{[OH_3^+]_2}{[OH_3^+]_1} \tag{3}$$

This is not an exact thermodynamic equation, and its justification rests more on empirical observation than on theory. It is the more reliable, the more nearly the two solutions resemble each other. It is still more reliable, but of more limited range of application, if the salt bridge (the saturated KCl) is omitted, and both solutions contain the same large concentration of the same electrolyte.[4]

It is usual in practice with aqueous solutions to split the cell into two others

$$\text{Hg, HgCl, sat. KCl, Soln. 1, } H_2 \text{, Pt}$$
$$\text{Hg, HgCl, sat. KCl, Soln. 2, } H_2 \text{, Pt}$$

the difference of whose potentials $E_2 - E_1$ must equal the potential E of equation (3). The potential of cell 1 is measured once for all with a solution of known oxonium-ion concentration, from which the potential E_0 of a similar cell containing oxonium ion at unit concentration is calculated. For any solution 2 it then follows that

$$E_2 = E_0 + \frac{RT}{F} \ln [OH_3^+]_2 \tag{4}$$

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[4] Brønsted, *Kgl. Danske Videnskab. Selskab, Math.-fys. Medd.*, **3**, No. 9 (1920).

Hydroxyl-ion Concentration.—The determination of the hydroxyl-ion concentration of aqueous solutions uses sodium hydroxide or other strong base as a reference point. The application of the indicator or the electrometric method depends upon the use of the law of equilibrium involving the ionization of water

$$2H_2O \rightleftharpoons OH_3^+ + OH^- \tag{II}$$

$$[OH_3^+][OH^-] = K_w = \frac{Ka_{H_2O}^2}{f_{OH_3^+}f_{OH^-}} \tag{5}$$

Consequently, oxonium-ion and hydroxyl-ion concentrations vary inversely and

$$\frac{[OH_3^+]_1}{[OH_3^+]_2} = \frac{[OH^-]_2}{[OH^-]_1} \tag{6}$$

provided the f's are constant.

Quantitative Treatment of Protolytic Equilibria.—It is customary and convenient to work with both ion concentrations and equilibrium constants in terms of their negative logarithms. Thus the pH of a solution is given by

$$pH = -\log [OH_3^+] \tag{7}$$

and to any equilibrium constant K there corresponds a pK given by

$$pK = -\log K \tag{8}$$

For every conjugate acid-base system present there is set up in aqueous solution an equilibrium of the type

$$HC_2H_3O_2 + H_2O \rightleftharpoons OH_3^+ + C_2H_3O_2^- \tag{III}$$

or

$$NH_4^+ + H_2O \rightleftharpoons OH_3^+ + NH_3 \tag{IV}$$

Regardless of charge type the equilibrium constant of this reaction is called the *acidity constant* of the acid-base system or of the acid for short.[5] Thus the acidity constant of acetic acid is given by

$$K_a = \frac{[OH_3^+][C_2H_3O_2^-]}{[HC_2H_3O_2]} \tag{9}$$

[5] Brønsted, *Chem. Rev.*, **5**, 231 (1928).

that of ammonium ion by

$$K_a = \frac{[OH_3^+][NH_3]}{[NH_4^+]} \tag{10}$$

The reciprocal of the acidity constant of an acid is called the *basicity constant* of the conjugate base.

The acidity constant of an acid of the acetic acid or $H_2PO_4^-$ type is identical with the ionization constant K_i of the Arrhenius theory; the acidity constant of an acid of the ammonium-ion type is identical with the hydrolysis constant of ammonium chloride or nitrate in that theory. The ionization constant of a base of the ammonia type is, however, given by

$$K_i = \frac{[NH_4^+][OH^-]}{[NH_3]} \tag{11}$$

It is related to the basicity constant K_b of ammonia and the acidity constant K_a of ammonium ion by the equations

$$K_b = \frac{1}{K_a} = \frac{K_i}{K_w} \tag{12}$$

as may easily be shown from equations (5) and (10).

Other Solvents: Lyonium and Lyate Ions.—A procedure of the same sort as that used in aqueous solution may be applied to any other *amphiprotic* solvent, *i.e.*, to any solvent that can add a proton to form a *lyonium*[6] ion or lose a proton to form a *lyate* ion. The lyonium and lyate ions of water are oxonium and hydroxyl ions; those of ethyl alcohol are ethyloxonium, $C_2H_5OH_2^+$, and ethoxide, $C_2H_5O^-$, ions; in acetic acid they are $CH_3C(OH)_2^+$ and $CH_3CO_2^-$; in ammonia ammonium and amide ions, NH_4^+ and NH_2^-; in sulfuric acid, $H_3SO_4^+$ and HSO_4^-. For solutions of constant ionic strength in any solvent the product of the concentrations of lyonium and lyate ions is a constant, the *autoprotolysis* constant of the solvent. This constant, the known values of which are listed in Table I, determines the range of values of acidity available in a solvent. Thus if one limits the magnitude of salt effects by using not over 0.1m solutions, the most acid solution possible in water has an oxonium-ion

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TABLE I.—AUTOPROTOLYSIS CONSTANTS

Solvent	pK
Water, 25°...	14.0
Water, 100°..	12.3
Formic acid 25°[2b,17].................................	6.2
Methanol, 25°[7]......................................	16.7
Ethanol, 25°[8].......................................	19.1
Ammonia, −33.4°[9].	22

concentration of 0.1; the most basic solution possible has a hydroxyl-ion concentration of 0.1, and, as the autoprotolysis constant is 1×10^{-14}, an oxonium-ion concentration of 10^{-13}. In formic acid with an autoprotolysis constant of 6×10^{-7} the corresponding range of values of the lyonium-ion concentration is only 0.1 to 6×10^{-6}.

The strength of an acid *in a given solvent* is measured by the extent of the reaction

$$HA + S \rightleftharpoons SH^+ + A^- \qquad (V)$$

in which HA is the acid, S the solvent, and SH$^+$ the lyonium ion. Obviously, this depends quite as much on the basicity of the solvent as it does on the acidity of the acid. Unfortunately, it depends also upon the nature of the medium in which the reaction occurs, and this is different for each solvent. Some of the medium effects are more or less predictable. Thus the fact that reaction (V) converts neutral molecules to ions implies that a high dielectric constant favors the ionization (page 90). In addition, however, there may be entirely unpredictable and specific interactions between solvent and acid and solvent and ion. Consequently, one cannot hope to set up a table of absolute strengths of acids or of bases that will lead to quantitative and reliable predictions of the effect of solvent upon ionization: the most that can be expected is a qualitative order of strengths from which the deviations may be relatively minor ones.

The Leveling Effect of the Solvent.—The range of acid strengths that may be measured in any one solvent is limited by

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[7] BJERRUM, UNMACK, and ZECHMEISTER, *Kgl. Danske Videnskab. Selskab, Math.-fys. Medd.*, **5**, No. 11 (1925).

[8] DANNER, *J. Am. Chem. Soc.*, **44**, 2832 (1922).

[9] Estimated from data in Franklin, "The Ammonia System of Compounds," New York, 1935, Chap. I.

a leveling effect of the solvent.[10] If the equilibrium constants of reaction (V) for two acids have the values of 100 and 1,000,000, the second acid is many times stronger than the first. Yet a 0.1M solution of the first will react until the concentration of molecular acid is 10^{-4}M, an amount too small to detect; its ionization seems, therefore, as complete as that of the second solution of which contains only 10^{-8}M molecular acid. Any acid the ionization constant of which in a given solvent exceeds a certain minimum (*ca* 100) is, therefore, a "strong acid" and is indistinguishable in strength from other strong acids.

The relative strengths of a series of acids cannot be measured, therefore, if the basicity of the solvent is too great; too acid a solvent is equally unfavorable. The measurement of the acid strength depends ultimately in every case upon the determination of the extent to which the acid reacts with a base, which may be the solvent in a conductivity or electrometric measurement or an indicator base. In so doing it must compete with the solvent acting as an acid, and if the latter is too strong an acid the reaction of the solute becomes too small to be measured. It is for this reason that inherently very strong acids like the sulfonic acids show no appreciable ionization when dissolved in sulfuric acid.

Relative and Absolute Values of Acidity.—The ratio of the acidities, *i.e.*, the concentrations of lyonium ion, of two solutions in a given solvent may be determined without much difficulty by the indicator or by the electrometric method, and the determination does not require a knowledge of the actual concentration of the lyonium ion in either solution. If such measurements are made in buffer solutions of two different conjugate acid-base systems, the ratio of the acidity constants follows immediately from the ratio of the acidities and the buffer concentrations, provided only that the ionization of the acid or the base is not too large. Consequently, the relative strengths of a series of acids or bases in a solvent may be determined without knowing the absolute ionization constant of any of them.

Measurements in Solvents of Low Dielectric Constant.—Since the range of acidities that may be investigated in a given solvent

[10] HANTZSCH, *Z. Elektrochem.*, **29**, 221 (1923).

decreases as the autoprotolysis constant increases, a solvent with a very low autoprotolysis would seem to be the ideal one for the investigation of acid and base strengths. Unfortunately, all the known solvents of this sort have low dielectric constants; they are not good solvents for electrolytes; and such electrolytes as do dissolve are present to a large extent as ion pairs, triplets, and higher polymers, the extent of association varying from electrolyte to electrolyte in an unpredictable fashion (page 52).

It is, therefore, not surprising that the law of equilibrium does not apply in a simple form to the reaction of a partly neutralized acid with an indicator in benzene[11] (dielectric constant 2.26) or chlorbenzene[12] (10.95). The reaction is

$$HA + I^- \rightleftharpoons A^- + HI \qquad (VI)$$

with HA the acid and HI the indicator acid. If one identifies the concentration of A^- with the stoichiometric concentration of the salt, the law of equilibrium in the form

$$\frac{[A^-][HI]}{[HA][I^-]} = K \qquad (13)$$

fails, but an empirical expression[11]

$$\left\{\frac{[A^-]}{[HA]}\right\}\left\{\frac{[HI]}{[I^-]}\right\}^n = K \qquad (14)$$

in which the nonintegral exponent n varies from case to case, does hold excellently. The values of K for a series of acids and the same indicator may be taken approximately as measures of the acid strengths.

To some extent, the difficulties encountered in low dielectric constant solvents may be expunged by loading the solution with a large and constant concentration of inert electrolyte, the same stratagem that proves so successful in suppressing salt effects in aqueous solutions (page 94). Thus in n-butyl alcohol ($\epsilon = 17.4$) the theoretical relation between electrometric acidity and the ratio of the concentrations of an acid and its conjugate base is obtained in solutions containing 0.05M lithium chloride with all other electrolytes present at concentrations that do not exceed

[11] LaMer and Downes, *J. Am. Chem. Soc.*, **55**, 1840 (1933).
[12] Griffiths, *J. Chem. Soc.*, 818 (1938).

0.0025M.[13] The procedure requires that an electrolyte be found which is sufficiently soluble in the medium and the ions of which have negligible acidity and basicity. This is not always practicable.
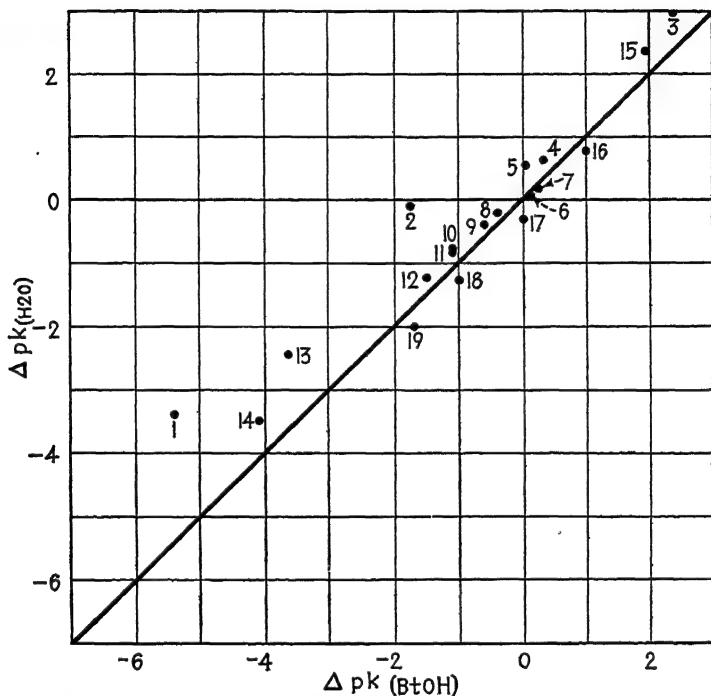
FIG. IX-1.—Relative strengths of acids in water and in *n*-butyl alcohol referred to benzoic acid: 1, picric; 2, 2,4-dinitrophenol; 3, *p*-nitrophenol; 4, butyric; 5, acetic; 6, *m*-toluic; 7, *p*-toluic; 8, *p*-chlorobenzoic; 9, *m*-chlorobenzoic; 10, *m*-nitrobenzoic; 11, *p*-nitrobenzoic; 12, salicylic; 13, maleic (1); 14, trichloroacetic; 15, maleic (2); 16, trimethylacetic; 17, *o*-toluic; 18, *o*-chlorobenzoic; 19, *o*-nitrobenzoic.[13]

The Effect of the Solvent upon the Relative Strengths of Acids.
The relative strengths of a series of acids of a given charge type in one solvent are simply and quantitatively related to those in another only in the limited case of meta and para substituted benzoic acid derivatives (page 207). The extent of the scatter in the more general case is indicated in Fig. 1 in which the

[13] WOOTEN and HAMMETT, *J. Am. Chem. Soc.*, **57**, 2289 (1935).

logarithms of the relative strengths of a series of acids in water are plotted against the corresponding values in n-butyl alcohol.[13] Had the relative strengths been the same in the two solvents, all the points would have lain on a single straight line. A very similar situation arises when the relative strengths of a series of acids in m-cresol ($\epsilon = 13$) are compared with the values in water.[14]

Even in a solvent with so low a dielectric constant as benzene, the estimates that may be made of relative acid strength by means of equation (14) place acids of a single charge type in the same order as in water, as the data of Table II demonstrate. A similar order appears in chlorobenzene.[12]

TABLE II.—RELATIVE ACID STRENGTH IN WATER AND IN BENZENE[11]

Acid	pK water	pK benzene
Trichloracetic	0.7	0.7
Dichloracetic	1.30	1.75
Chloracetic	2.86	2.90
Salicylic	3.00	2.55
Formic	3.75	3.64
Benzoic	4.20	4.58
Acetic	4.75	5.18

Changes that alter the reacting group profoundly have a large effect on the precision of such parallelisms. Thus the increase in pK in passing from water to ethanol is 1.8 and 1.2 units less for the phenols picric acid and 2,4-dinitrophenol than it is on the average for carboxylic acids.[15] (Evidence of a similar situation appears in Fig. 1.) The effect of a change in charge type is large and in the direction expected, acids of the type of ammonium ion averaging 0.8 logarithmic unit stronger in ethanol than in water, whereas acids of the electrically neutral carboxylic type average 5.0 units weaker. For reactions of the type

$$BH^+ + S \rightleftharpoons B + SH^+ \tag{VII}$$

the effect of dielectric constant should be small, for there is no

[14] BRØNSTED, DELBANCO, and TOVBORG-JENSEN, *Z. physik. Chem.*, **A169**, 361 (1934).

[15] DEYRUP, *J. Am. Chem. Soc.*, **56**, 60 (1934).

change in the number of ions; the increase in acidity indicates that the solvent ethanol is more basic than the solvent water. The decrease in acidity of the neutral acids on transfer from water to alcohol is, therefore, a dielectric constant effect which hinders the formation of ions according to equation (V).

Very Strong and Very Weak Acids.—With respect to acids that are too strong for measurement in water, investigation in other solvents has led to the following information. In methanol and ethanol,[16] HCl, HBr, HI, $HClO_4$, $C_2H_5OSO_3H$, and $C_6H_5SO_3H$ are still strong; nitric acid with a pK of 3.57[15] is decidedly weak; HIO_3 and HCNS are also measurably weak. All the foregoing acids except perchloric become weak in acetone, nitrobenzene, and nitromethane. Perchloric acid is, therefore, by all odds the strongest acid known, as was early appreciated by Hantzsch.[10] HCl is incompletely ionized in the solvent formic acid, whereas sulfuric acid is strong and benzenesulfonic acid nearly so.[2b,17] The order of strength of the common strong acids is, therefore, from stronger to weaker, $HClO_4$, H_2SO_4, $C_6H_5SO_3H$, HCl, HNO_3. Solutions of strongly electrophilic halides like boron fluoride, aluminum chloride, or zinc chloride may be quite as acid as those of a strong acid (page 62).

The data on the ionization of acids are also informative on the ionizing power toward electrically neutral acids of the various solvents involved. This ionizing power is a function both of the basicity of the solvent and of its dielectric constant. In this sense acetone, nitrobenzene, and nitromethane have little ionizing power, alcohol is poorer than water, formic acid poorer yet. Liquid ammonia in which carboxylic acids are completely ionized (page 52) is the best ionizing solvent for acids known; sulfuric acid is one of the poorest. Unfortunately, sulfuric and formic acids, the only solvents of materially lower basicity than water which have high dielectric constants, have such large autoprotolytic constants that the range of acidities which may be measured in either of them is very limited, and there is a large gap between them.

[16] Murray-Rust and Hartley, *Proc. Roy. Soc.* (London), **A126**, 84 (1929). Wright, Murray-Rust, and Hartley, *J. Chem. Soc.*, 199 (1931). Murray-Rust, Hadow, and Hartley, *ibid.*, 215 (1931).

[17] Hammett and Deyrup, *J. Am. Chem. Soc.*, **54**, 4239 (1932).

Liquid ammonia, although it is a solvent in which there is considerable ion association, is probably the best one available for the study of very weak acids. The only considerable amount of data on such substances (page 50) was, however, derived from the study of ether solutions.

The Measurement of the Strengths of Very Weak Bases.—The problem of the choice of solvent for the investigation of bases is analogous to that in the case of acids. If the solvent is too basic, the ionization of the solute base will be too small to be detected; if it is too acid, the ionization will be practically complete and the strength of the base will be indeterminable; if the dielectric constant is low, the multitudinous difficulties arising from limited solubilities and ion association complicate the situation. A large number of bases that are on the upper edge of the range accessible to measurement in water have been studied in acetic acid.[18] Bases for which the negative logarithm of the acidity constant of the conjugate acid, pK_a, is greater than 5 in water, for which, therefore, the basic ionization constant is greater than 10^{-9}, are practically completely ionized in acetic acid. Bases the strength of which is measurable in both solvents show relative strengths in the one solvent that closely parallel those in the other.

The Base Strength of Water.—It has been known for a long time that water has the properties of a base in the solvent ethanol,[19] and both indicator methods and those depending upon the effect of water on acid-catalyzed reactions have been used to determine the extent of its ionization

$$H_2O + C_2H_5OH \rightleftharpoons OH_3^+ + C_2H_5O^-$$ (VIII)
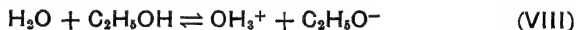
The best value for pK_a is 0.8, which makes it a thousandfold weaker base than aniline, and the value of pK_i, where K_i is the ionization constant, is 18.3.[15]

The base strength of water in formic acid[17] is measured by a pK_i of 4.78 and a pK_a of 1.4.

Principles of Acidity Measurements in Mixed Solvents.—The problem of finding a solvent in which a weak base is measurably

[18] HALL, *J. Am. Chem. Soc.*, **52**, 5115 (1930).
[19] FITZGERALD and LAPWORTH, *J. Chem. Soc.*, **93**, 2163 (1908). GOLDSCHMIDT, *Z. physik. Chem.*, **89**, 129 (1914).

but not too largely ionized may be solved by using a mixture of solvents, but the solution brings its own not insuperable difficulties. As many bases that do not ionize measurably in water are practically completely ionized in sulfuric acid, there must be mixtures of sulfuric acid and water in which the extent of ionization is measurable: the problem is to measure it. Most of the usual methods of determining the extent of ionization of a solute involve the measurement of some property of the solution as a whole such as the conductivity or the electrometric or indicator pH. But when a small amount of a base B is introduced into a mixture of sulfuric acid and water in which, as a result of the reaction

$$H_2SO_4 + H_2O \rightleftharpoons OH_3^+ + HSO_4^- \tag{IX}$$
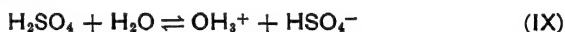
both conductivity and oxonium-ion concentration are very large, the change in conductivity or in oxonium-ion concentration which results from the ionization of the base

$$B + OH_3^+ \rightleftharpoons BH^+ + H_2O \tag{X}$$

will not be detectable. Some specific difference in the properties of the base and of its conjugate acid, such as the change in light absorption that usually accompanies a reaction of this sort, must, therefore, be employed.

There is a further difficulty in the fact that the nature of the medium changes as the proportions of sulfuric acid and water are altered, which means that equilibrium laws written in terms of concentrations instead of activities are no longer applicable. The following analysis[20] shows, however, that errors due to this difficulty may be canceled out by a suitable treatment. In this, the strength of an electrically neutral base B is measured by the acidity constant of its conjugate acid, expressed in terms of activities instead of concentrations

$$pK_a^B = -\log \frac{a_{H^+} a_B}{a_{BH^+}} \tag{15}$$

The activities are referred to dilute aqueous solutions; *i.e.*, the activity coefficients are made to approach unity in dilute aqueous

[20] HAMMETT and DEYRUP, *J. Am. Chem. Soc.*, **54**, 2721 (1932). HAMMETT, *Chem. Rev.*, **16**, 67 (1935).

solution; they do not then necessarily approach unity in dilute solutions in another solvent. Further, the activity of protons or hydrogen ions is so defined that it approaches the concentration of oxonium ion in dilute aqueous solution. Consequently, in *dilute aqueous solution*

$$pK_a^{\text{B}} = pH - \log \frac{c_{\text{B}}}{c_{\text{BH}^+}} \tag{16}$$

If B is an indicator the ionization of which in dilute aqueous solution is of such a magnitude that the indicator ratio $c_{\text{B}}/c_{\text{BH}^+}$ may be measured colorimetrically, the quantity pK_a^{B} is immediately obtained, since the oxonium-ion concentration and pH of such solutions are easily determined.

If C is another base for which

$$pK_a^{\text{C}} = - \log \frac{a_{\text{H}^+}a_{\text{C}}}{a_{\text{CH}^+}} \tag{17}$$

and if C is a sufficiently weaker base than B, but not too weak, then a solvent in the region of 10 per cent sulfuric acid may be found in which the ionization of both B and A is measurable. If a small amount of B is added to one portion of this solvent and a small amount of C to another, the values of the quantity a_{H^+} in the two solutions will not differ appreciably, being practically identical with that of the solvent in the absence of the indicator. Consequently

$$pK_a^{\text{C}} - pK_a^{\text{B}} = - \log \left(\frac{a_{\text{C}}}{a_{\text{CH}^+}} \right) + \log \left(\frac{a_{\text{B}}}{a_{\text{BH}^+}} \right) \tag{18}$$

$$= - \log \left(\frac{c_{\text{C}}}{c_{\text{CH}^+}} \right) + \log \left(\frac{c_{\text{B}}}{c_{\text{BH}^+}} \right) - \log \left(\frac{f_{\text{C}}f_{\text{BH}^+}}{f_{\text{CH}^+}f_{\text{B}}} \right)$$

There are both experimental and theoretical reasons for believing that the term involving the f's may be neglected in solutions of high dielectric constant.

Since the pK's are thermodynamic quantities the values of which are independent of the nature of the medium, the constancy of the activity coefficient term is proved if the quantity $- \log (c_{\text{C}}/c_{\text{CH}^+}) + \log (c_{\text{B}}/c_{\text{BH}^+})$ is constant. Experimentally, this turns out to be the case, not only for the range of sulfuric

acid solutions, say 8 to 12 per cent, in which the quantity can be measured, but also for mixtures of perchloric, nitric, and hydrochloric acids with water, for solutions in the solvent formic acid, and for moderately concentrated solutions of sulfuric acid in acetic acid. The corresponding quantity for other pairs of indicators in other regions of sulfuric acid-water mixtures and other strong acid systems has also been shown to be constant. As the activity coefficient term is constant and its value is zero in dilute aqueous solution, in which all the f's equal unity, it must be zero in all solutions.

That this should be the case is not difficult to understand. By adding and subtracting log $c_{OH_3^+}$, the expression

$$- \log \left(\frac{c_C}{c_{CH^+}} \right) + \log \left(\frac{c_B}{c_{BH^+}} \right)$$

is converted to

$$- \log \left(\frac{c_{OH_3^+} c_C}{c_{CH^+}} \right) + \log \left(\frac{c_{OH_3^+} c_B}{c_{BH^+}} \right),$$

which is the difference in the logarithms of the acidity constants in terms of concentrations of the two acids CH^+ and BH^+, *i.e.*, the logarithm of the acidity constant of BH^+ relative to that of CH^+. Such relative acidity constants are known (page 81) to be functions of the dielectric constant of the type

$$- \log \left(\frac{c_{OH_3^+} c_C}{c_{CH^+}} \right) + \log \left(\frac{c_{OH_3^+} c_B}{c_{BH^+}} \right) = a + \frac{b}{\epsilon}$$

with values of the coefficients b such that the expression is practically constant and equal to a when the dielectric constant is of the order of 80 or more.

It follows, therefore, that with considerable precision for solutions of high dielectric constant, and approximately for any solution,

$$pK_a^C - pK_a^B = - \log \left(\frac{c_C}{c_{CH^+}} \right) + \log \left(\frac{c_B}{c_{BH^+}} \right) \qquad (19)$$

If now an indicator D can be found the range of which overlaps that of C in the same way as the latter overlaps B, so that the extent of ionization of both C and D may be measured in 20 per

cent sulfuric acid or some similar medium, then

$$pK_a^D - pK_a^C = -\log\left(\frac{c_D}{c_{DH^+}}\right) + \log\left(\frac{c_C}{c_{CH^+}}\right) \qquad (20)$$

Since pK_a^C is known from equation (19), pK_a^D is then also known.

Base Strengths of Indicators for Highly Acid Systems.—By this stepwise method it is possible to measure the strengths of successively weaker indicators in sulfuric acid-water mixtures extending up to the anhydrous acid. The values of pK_a thus obtained are listed in Table III along with similar results obtained in other mixtures of strong acids with water and in anhydrous formic acid. For each solvent the value enclosed in parentheses served as a reference point. Thus the value of aminoazobenzene

TABLE III.—INDICATOR CONSTANTS (pK_a) OF VERY WEAK BASES[20,21]

Indicator	Solvent				
	HCl H₂O	HNO₃ H₂O	H₂SO₄ H₂O	HClO₄ H₂O	HCO₂H
Aminoazobenzene.........	(+2.80)				
Benzeneazodiphenylamine	+1.52				
p-Nitroaniline............	+1.11	(+1.11)	(+1.11)	(+1.11)	
o-Nitroaniline............	−0.17	−0.20	−0.13	−0.19	(−0.17)
p-Chlor-o-nitroaniline.....	−0.91	−0.97	−0.85	−0.91	−0.94
p-Nitrodiphenylamine....	....	....	−2.38	....	−2.51
2,4-Dichlor-6-nitroaniline..	....	....	−3.22	−3.18	−3.31
p-Nitroazobenzene........	....	....	−3.35	−3.35	−3.29
2,6-Dinitro-4-methylaniline	....	....	−4.32		
2,4-Dinitroaniline........	....	....	−4.38	−4.43	
N,N-Dimethyl-2,4,6-trinitroaniline..........			−4.69		
Benzalacetophenone......			−5.61		
β-Benzoylnaphthalene....			−5.92		
p-Benzoyldiphenyl........			−6.19		
6-Brom-2,4-dinitroaniline..			−6.59		
Anthraquinone...........			−8.15		
2,4,6-Trinitroaniline......	....	....	−9.29		

is based upon its colorimetrically measured ionization in very dilute HCl solutions, and the values of the other indicators listed

[21] HAMMETT and PAUL, *J. Am. Chem. Soc.*, **56**, 827 (1934).

for HCl solutions are derived from this by stepwise comparison. The value for *p*-nitroaniline thus obtained serves as a starting point for the other strong acids, and the average value for *o*-nitroaniline found in these solutions is the reference point for solutions in formic acid.

The substances listed have all been shown by the freezing-point method (page 45) to ionize as simple bases in sulfuric acid according to the equation

$$B + H_2SO_4 \rightleftharpoons BH^+ + HSO_4^-$$ (XI)

Substances like triphenylcarbinol the ionization process of which is more complicated (page 54) are unsuited for use as indicators in such systems as these because the extent of ionization depends upon the activity of water in the solution.

The only serious difficulty in carrying out these determinations arises from the fact that the light absorption of a solute changes with the nature of the medium in which it is dissolved. Even though this "medium effect" is of much smaller magnitude than the large changes that accompany the conversion of a base to its conjugate acid, it must be corrected for. The consistency of the results, especially the fact that the relative strength of two bases is independent of the medium in which they are compared, demonstrates that the correction can be satisfactorily accomplished.

The Acidity Function H_0.—With the information obtained in the study of these indicators it becomes possible to define an acidity function which just as definitely expresses the tendency of a solution to transfer a proton to a neutral base as the quantity pK_a measures the tendency of the base to accept a proton. This function H_0 is defined by the equation

$$H_0 = -\log\left(\frac{a_{H^+}f_B}{f_{BH^+}}\right)$$ (21)

It depends, therefore, upon the activity of hydrogen ion and also upon the ratio of the activity coefficients of a neutral base and its conjugate acid. As the indicator experiments showed that all quantities of the type $f_B f_{CH^+}/f_{BH^+} f_C$ have the value unity, which is possible only if the ratio f_B/f_{BH^+} has the same value for all bases, the acidity function has a value independent

of the base used for its measurement and is a characteristic property of the solution.

By combining equation (21) with (15) and remembering that $f = a/c$, one obtains an alternative expression for H_0

$$H_0 = pK_a + \log\left(\frac{c_B}{c_{BH^+}}\right) \qquad (22)$$

which furnishes a method for its experimental determination. All that is necessary is to add an indicator the value of pK_a of
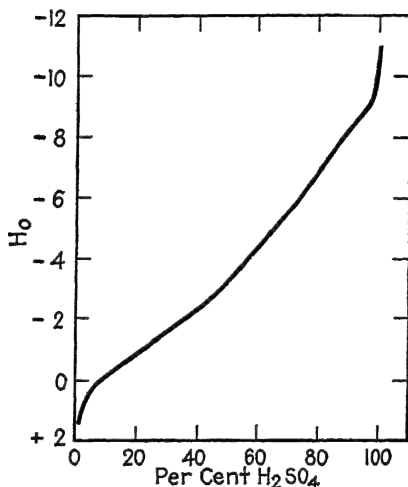
Fig. IX-2.—Acidity function of H_2SO_4-H_2O solutions.[20,21]

which is known and to measure the indicator ratio c_B/c_{BH^+} colorimetrically. Values of H_0 for sulfuric acid solutions are plotted against the percentage composition in Fig. 2 and are

TABLE IV.—ACIDITY FUNCTIONS H_0 FOR SULFURIC ACID WATER MIXTURES[20,21]

% H_2SO_4	H_0	% H_2SO_4	H_0	% H_2SO_4	H_0	% H_2SO_4	H_0
5	+0.24	30	−1.54	55	−3.79	80	− 6.82
10	−0.16	35	−1.90	60	−4.32	85	− 7.62
15	−0.54	40	−2.28	65	−4.89	90	− 8.17
20	−0.89	45	−2.72	70	−5.54	95	− 8.74
25	−1.22	50	−3.23	75	−6.16	100	−10.60

tabulated for round concentrations in Table IV. The values for perchloric acid solutions up to 70 per cent are nearly identical with those for sulfuric acid of the same concentration. Values for moderately concentrated solutions of these and other strong acids are plotted in Fig. 3.

The acidity function is not identical with the pH, it merely becomes equal to it in dilute aqueous solution. Neither is it equal to $-\log a_{H^+}$, which is an essentially undeterminable
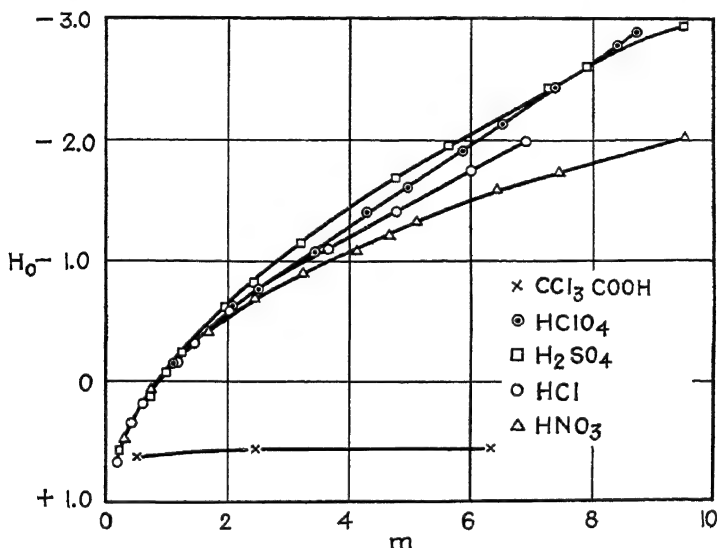
Fig. IX-3.—Acidity functions of moderately concentrated aqueous acids.[21]

quantity. Although the value of H_0 measures the tendency of a solution to transfer a proton to a neutral base like *p*-nitroaniline or anthraquinone, it does not at all measure the tendency to do the same thing to a base of any other electrical charge. The tendency to transfer a proton to a base with a single negative charge is, for instance, measured by another acidity function H_-, which is defined by the equation

$$H_- = -\log \frac{a_{H^+}f_{B^-}}{f_{HB}} \qquad (23)$$

and the values of which may be determined by the use of indicators like *p*-nitrophenol and picric acid. The values of H_0 and

H_- may be very different, thus the magnitude of the former in ordinary glacial acetic acid is in the neighborhood of $+3.5$, that of the latter is a negative number of considerable magnitude. Because the acidity function is defined in such a way as to become identical with the pH in dilute aqueous solution, and because the latter involves the negative logarithm of the oxonium-ion concentration, a large negative value of H_0 implies a high acidity. Further as pK_a is defined in terms of the negative logarithm of the acidity constant, a large negative value implies a very weak base.

The idea of an acidity that increases continuously from water to sulfuric acid offers considerable difficulty to those schooled in the aquocentric theory of ionization which grew out of Arrhenius' great discoveries. In that theory much was made of the fact that metals and insoluble substances like calcium carbonate do not dissolve in pure anhydrous acids or in their solutions in solvents like benzene; a general parallelism between conductivity and acidity was frequently assumed. The data from reactions of solids have, however, no bearing on the problem, because the vital factor in their occurrence or suppression is so often the formation of an impervious and insoluble coating. Thus it is common knowledge that cast iron is a useful material in which to carry out reactions in strong sulfuric acid, whereas the metal dissolves readily in dilute acid. But the reason it does not dissolve in the strong acid is because it is passive, which means that it has become covered with an impervious and insoluble layer of oxide.[22] Such phenomena have nothing whatsoever to do with the acidity of the solutions. As for the conductivity of sulfuric acid-water systems, this is due to the ions that are produced by the reaction

$$H_2SO_4 + H_2O \rightleftharpoons OH_3^+ + HSO_4^- \qquad (IX)$$
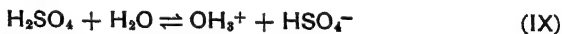
At one end of the scale of compositions the extent of this reaction is limited by the amount of sulfuric acid present, at the other by the amount of water; consequently, the conductivity rises to a maximum in the intermediate region.[23] The maximum does not

[22] EVANS, J. Chem. Soc., 1020 (1927).
[23] HALL and VOGE, J. Am. Chem. Soc., 55, 239 (1933).

appear at the equimolal mixture, presumably because of the important influence that viscosity exerts upon conductivity.

For some purposes it is convenient to define another function h_0 related to H_0 in the same way that oxonium-ion concentration is to pH, *viz.*,

$$H_0 = - \log h_0 \tag{24}$$

It follows that

$$h_0 = \frac{a_{H^+} f_B}{f_{BH^+}} \tag{25}$$

The Determination of the Strength of Very Weak Bases.—
The strength of weak bases which are not indicators in the ordinary sense may be determined when the base and its conjugate acid differ appreciably in their ultraviolet absorption.[24] This is nearly always the case with aromatic compounds. The principle of the method is the same as that used with indicators, the absorption in the ultraviolet being used instead of that in the visible region of the spectrum. In practice, it is of course relatively tedious, and the correction for the medium effect is somewhat more difficult to apply. The values of pK_a obtained by the method of ultraviolet absorption are listed in Table V.

TABLE V.—STRENGTHS (pK_a) OF WEAK BASES FROM ULTRAVIOLET
ABSORPTION[24,25]

Benzoic acid	−7.26	p-Bromacetophenone	−6.40
Phenylacetic acid	−7.59	Propiophenone	−6.28
Acetophenone	−6.03	n-Butyrophenone	−6.21
p-Methylacetophenone	−5.35	i-Butyrophenone	−6.72

The typical carbonyl compound acetophenone is, therefore, a weaker base than aniline by a factor of nearly 10^{-10}, it is a little weaker than dinitroaniline, but over a thousand times stronger than trinitroaniline. Its strength is not very different from that of other simple phenyl ketones, but it is over ten times stronger than benzoic acid and over one hundred times stronger than anthraquinone. Substitution of methyl or bromine in the

[24] FLEXSER, HAMMETT, and DINGWALL, *J. Am. Chem. Soc.*, **57**, 2103 (1935).

[25] FLEXSER and HAMMETT, *J. Am. Chem. Soc.*, **60**, 885 ,(1938). ZUCKER and HAMMETT, *ibid.*, **61**, 2785 (1939).

ring has a relatively large effect in the direction expected; substitution of methyl for hydrogen on the terminal methyl group has an opposite effect from that of methyl in the benzene ring. A solution of acetophenone in 0.1M aqueous hydrochloric acid is converted to its conjugate acid to the extent of only one part in ten million.
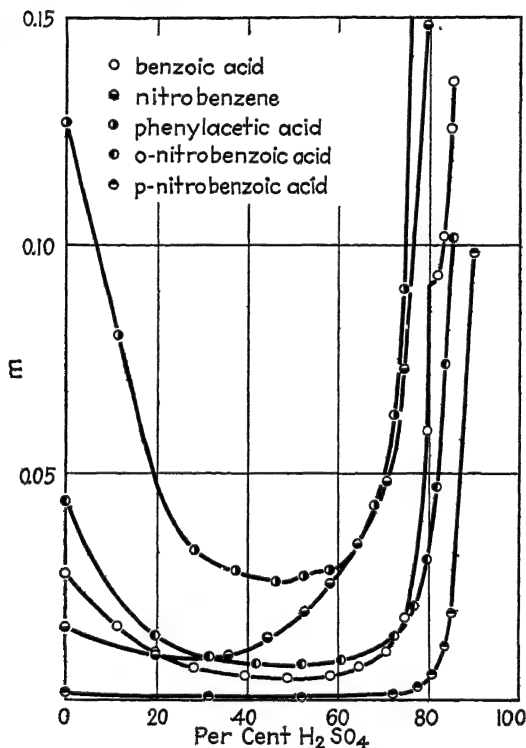
Fig. IX-4.—Solubilities of oxygen compounds in sulfuric acid-water mixtures.

In principle, any other physical property that changes by a sufficiently large amount when a base is converted to its conjugate acid might be employed for the determination of the base strength. So also might such a chemical property as the fraction of nitration in the meta position. This should, according to theory, increase upon the introduction of a positive charge into the molecule and is known to do so with benzal-

dehyde, acetophenone, and ethyl benzoate at acidities that convert these to their conjugate acids.[26]

The Solubility of Oxygen Compounds in Sulfuric Acid-water Mixtures.[27]—The solubility of organic oxygen compounds varies in a striking fashion with the composition of sulfuric acid-water mixtures. Some examples are shown in Fig. 4, in which the solubility in moles per 1000 g. solvent is plotted against percentage composition of the sulfuric acid-water solvent. Although the conversion of the base to the soluble conjugate acid is no doubt an important factor in the solubility increase at high acid concentrations, it cannot be the sole cause for the following reasons. Nitrobenzene is only partly ionized in pure sulfuric acid (page 47) and shows a rapid increase in solubility at acid concentrations at which, therefore, not more than one millionth of it can possibly be converted to the conjugate acid. Dinitrobenzene and trinitrotoluene are soluble but nonionized (page 47) in sulfuric acid, yet show a rapid increase in solubility with acid concentration.[28] Finally, the pK_a estimated for benzoic acid on the assumption that the solubility increase is due only to its basic properties is 1.4 units too low.[27] Obviously sulfuric acid may dissolve these substances by virtue of some other property than that of converting them to their conjugate acids.

Acidity Function and Reaction Rate.—Some acid-catalyzed reactions exhibit a simple relation between rate and acidity function in moderately concentrated solutions of strong acids.[29] This is notably so of the sucrose hydrolysis for which log k is plotted against H_0 in Fig. 5 for data that cover a thousandfold variation in specific rate. Except for the data on trichloracetic acid the agreement with a straight line of unit slope is excellent. For no other measure of acidity is any agreement found, the ratio of the rates in 4M and 0.1M HCl being, *e.g.*, 5.5 times greater than the ratio of the oxonium-ion concentrations. It follows, therefore, that the specific rate k is proportional to h_0, *i.e.*, to $a_{H^+} f_B / f_{BH^+}$. The cause of the deviation in the case of trichloracetic acid is not known, it might be due to esterification of the

[26] Baker, *J. Chem. Soc.*, 307 (1931); Baker and Hey, 1226; 2917 (1932).

[27] Hammett and Chapman, *J. Am. Chem. Soc.*, **56**, 1282 (1934).

[28] Hough, Savage, and van Marle, *Chem. Met. Eng.*, **23**, 666 (1920).

[29] Hammett and Paul, *J. Am. Chem. Soc.*, **56**, 830 (1934).

sucrose hydroxyls, yielding an ester more susceptible to hydrolysis than sucrose. A similar relation between rate and acidity function obtains in the hydrolysis of cyanamide in nitric acid solutions of concentrations up to 5м.[29]

On the other hand, the enolization of acetophenone[30] shows very poor correlation between specific rate and acidity function
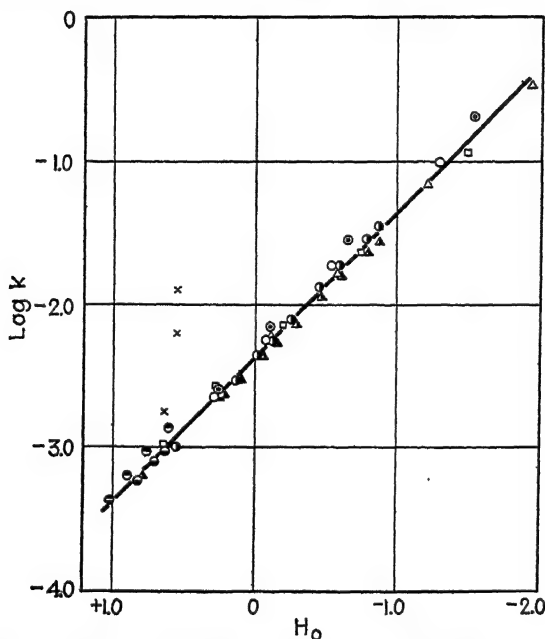
Fig. IX-5.—Relation between H_0 and velocity constant for hydrolysis of sucrose: ⊙, HClO₄ 0.5–4 M; □, H₂SO₄ 0.25–3.77 M; ○, HCl 0.5–4 M; △, HNO₃ 0.5–6.95 M; ×, CCl₃COOH 0.5–4 M, all from data of Hantzsch and Weissberger. ◑, HCl 0.28–3.08 M; ▲, HNO₃ 0.19–3.08 M, data of Armstrong and Wheeler and of Worley. ◐, 0.1 N HCl + KCl 0–3 M; ◑, 0.1 N HCl + BaCl₂ 0–1.3 M, data of Kautz and Robinson.[29]

but a satisfactory proportionality between rate and concentration of oxonium ion (*i.e.*, stoichiometric concentration of acid) in perchloric acid solutions up to 3.6м (Fig. 6). The behavior in sulfuric acid solutions is more complicated, presumably because bisulfate ion is a catalyst of considerable efficiency for this reaction. The correlation between rate and acidity function also

[30] ZUCKER and HAMMETT, *J. Am. Chem. Soc.*, **61**, 2791 (1939).

fails for the enolization of *m*-nitroacetophenone in sulfuric-acid-acetic-acid solutions.[31]

The difference between the behavior of the sucrose and cyanamide reactions, on the one hand, and the acetophenone reaction, on the other, may probably be attributed to the fact that the latter reaction shows a general acid catalysis while the sucrose reaction does not (unless the trichloracetic deviation is due to catalysis by the molecular acid). If the rate-determining step in the sucrose hydrolysis is a first-order reaction of the conjugate acid of sucrose, SH^+, the rate must be given by
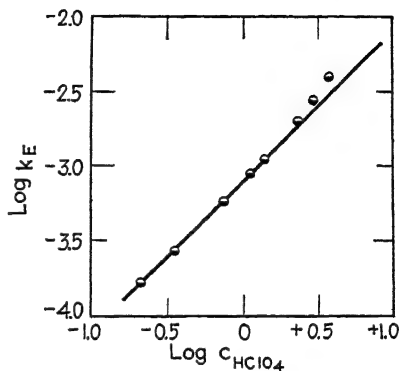
Fig. IX-6.—Relation between specific rate of enolization of acetophenone and concentration of perchloric acid.[30]

$$v = k_2[SH^+]\frac{f_{SH^+}}{f_{X^+}} \qquad (26)$$

in which f_{X^+} is the activity coefficient of the transition state. By the law of equilibrium

$$[SH^+] = K_a \frac{[S][OH_3^+]}{a_{H_2O}} \frac{f_S f_{OH_3^+}}{f_{SH^+}} \qquad (27)$$

hence

$$v = k_2 K_a \frac{[S][OH_3^+]}{a_{H_2O}} \frac{f_S f_{OH_3^+}}{f_{X^+}} \qquad (28)$$

and

$$k = k_2 K_a[OH_3^+]\frac{f_S f_{OH_3^+}}{f_{X^+} a_{H_2O}} = k_2 K_a a_{H^+}\frac{f_S}{f_{X^+}} \qquad (29)$$

By virtue of this and the definition of h_0 [equation (25)] the condition for proportionality between k and h_0 is that

$$\frac{f_S f_{BH^+}}{f_{X^+} f_B} = \text{constant} \qquad (30)$$

This is not unreasonable since it implies merely that the activity

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[31] PAUL and HAMMETT, *J. Am. Chem. Soc.*, **58**, 2182 (1936).

coefficient of the transition state, which is an activated complex of sucrose plus a proton, bears a ratio to that of sucrose which is affected by the medium in the same way as the ratio f_{BH^+}/f_B for any base.

In the enolization of acetophenone, a mobile and reversible conversion of the ketone K to its conjugate acid KH^+ is followed by a rate-determining conversion to the enol E

$$K + OH_3^+ \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} KH^+ + H_2O \qquad \text{(XII)}$$

$$KH^+ + H_2O \overset{k_2}{\rightarrow} E + OH_3^+ \qquad \text{(XIII)}$$
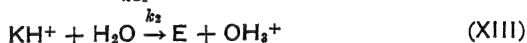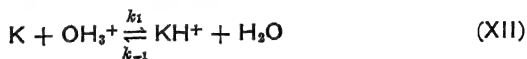
The rate equation is

$$v = k_2[KH^+]a_{H_2O}\frac{f_{KH^+}}{f_{X^+}} \qquad (31)$$

$$v = k_2K_1[K]a_{OH_3^+}\frac{f_K}{f_{X^+}} \qquad (32)$$

hence

$$k = k_2K_1[OH_3^+]\frac{f_K f_{OH_3^+}}{f_{X^+}} \qquad (33)$$

The necessary condition for the observed proportionality between k and $[OH_3^+]$ is therefore that

$$\frac{f_K f_{OH_3^+}}{f_{X^+}} = \text{constant} \qquad (34)$$

This is again not unreasonable, for the transition state has the structure (A)

$$\left[\begin{array}{c} \quad\quad H \quad\quad H \\ C_6H_5 - C - C\cdots H\cdots O \\ \quad\quad | \quad | \quad\quad\quad H \\ \quad\quad O \quad H \\ \quad\quad | \\ \quad\quad H \end{array} \right]^+$$

$$(A)$$
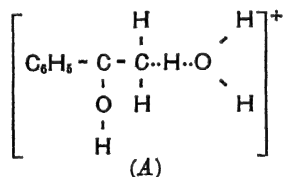
In addition to acetophenone and a proton this contains a water molecule that is in the course of becoming an oxonium ion. The two substances the activity coefficients of which appear in the numerator of equation (34) also contain acetophenone, a proton, and a water molecule, and this may be the reason that the ratio is constant.

On this theory the difference in the behavior of the sucrose reaction and the enolization arises from the presence of a molecule of the solvent in the transition state in the latter case. If this distinction can be upheld as a general one, it offers considerable promise as a tool for the investigation of reaction mechanisms.

Still other kinds of behavior appear in reactions for which particular acids are specific catalysts. Thus the rearrangement of *N*-chloracetanilide is specifically catalyzed by hydrochloric acid, other acids being comparatively ineffective (page 327). The chlorine part of the HCl must, therefore, be as important as the hydrogen part; for the same reason the rate varies with the activity of molecular HCl which is the same thing as the product of the activities of oxonium and chloride ions.[32] Since this varies approximately as the square of the stoichiometric concentration of acid, the reaction shows an especially rapid increase in rate with increasing acid concentration.

Reactions in the Solvent Sulfuric Acid.—The extension to more concentrated acid solutions of the study of reactions the rate of which is measurable in dilute ones reaches an early limit, either because the rate becomes unmeasurably large or because of a change in mechanism (page 231), and no kinetic data are available on reactions in the intermediate range of acid concentrations. At the high end of the range, however, a number of reactions that occur in dilute solutions in the solvent sulfuric acid have been extensively studied as examples of negative catalysis. Thus the decomposition of formic acid, the equation of which, usually written

$$HCO_2H \rightarrow CO + H_2O \qquad \text{(XIV)}$$
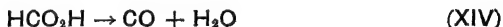
is more accurately expressed as

$$HCO_2H + H_2SO_4 \rightarrow CO + OH_3^+ + HSO_4^- \qquad \text{(XV)}$$

goes at a hundredfold smaller rate in 95 per cent sulfuric acid than in the pure acid.[33] Formally, this is a negative catalysis by water, no more so, however, than is the retardation produced by ammonia in the HCl catalyzed hydrolysis of sucrose in dilute aqueous solution. Water is a strong base in sulfuric acid, and

[32] HARNED and SELTZ, *J. Am. Chem. Soc.*, **44**, 1475 (1922).

[33] DE RIGHT, *J. Am. Chem. Soc.*, **55**, 4761 (1933).

the specific rate of the formic acid decomposition is directly proportional to the quantity h_0, as the plot of Fig. 7 demonstrates, the log k-H_0 plot being linear with unit slope.[34]   The reaction is, therefore, an acid-catalyzed one inhibited by the base water.   A more detailed analysis follows.
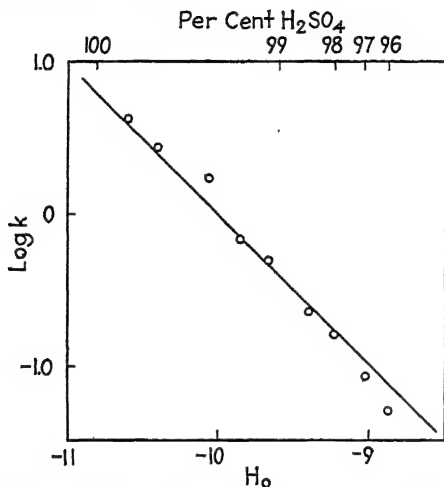
Fig. IX-7.—Relation between specific rate of the formic acid decomposition and the acidity function H_0.

Properties of Solutions in the Solvent Sulfuric Acid.[35]—Sulfuric acid differs from other amphiprotic solvents chiefly in the small magnitude of the interionic forces operating in it and the large magnitude of its autoprotolysis.   The first property is overwhelmingly evidenced by freezing point, solubility, and indicator data; according to theory it must result from a very high dielectric constant, although this has not been measured. By virtue of it one may treat activity coefficients as constants over the range from the pure solvent to an ionic strength of 3 or more.   Because of the large autoprotolysis, effects due to the presence of the lyonium and lyate ions of the solvent ($H_3SO_4^+$ and HSO_4^-) are much more important than they are, for instance,

[34] HAMMETT, *Chem. Rev.*, **16**, 67 (1935).

[35] (a) HAMMETT and DEYRUP, *J. Am. Chem. Soc.*, **55**, 1900 (1933).   (b) HAMMETT and LOWENHEIM, *ibid.*, **56**, 2620 (1934).   (c) TREFFERS and HAMMETT, *ibid.*, **59**, 1708 (1937).

in aqueous solution. There is also a dissociation of the solvent into SO_3 and H_2O, both of which react further to form ions as is evidenced by the marked increase in the conductivity of sulfuric acid produced by the addition of either.[36]

A plot of the freezing point of SO_3—H_2O mixtures in the neighborhood of the 1:1 mixture, *i.e.*, of pure H_2SO_4, is shown in Fig. 8, the temperatures being on an arbitrary scale.[35a] Starting from the freezing-point maximum which necessarily appears at the composition of pure H_2SO_4, the addition of water
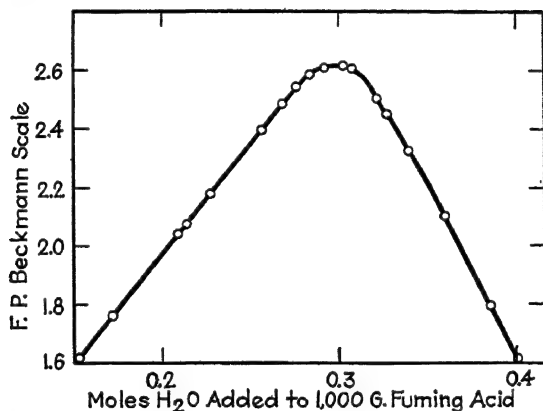
Fig. IX-8.—Relation between freezing point on an arbitrary scale and composition of SO_3-H_2O mixtures in the neighborhood of the composition of H_2SO_4.[35a]

produces a decrease in freezing point which, after a short curved section, is linear with a slope of 11.85 deg./mole., only 6 per cent less than that calculated for a binary strong electrolyte subject to no interionic forces. The initial curvature results from the autoprotolysis and the SO_3 decomposition. With respect to the former effect

$$2H_2SO_4 \rightleftharpoons H_3SO_4^+ + HSO_4^- \qquad \text{(XVI)}$$

the law of equilibrium takes the form for dilute solutions

$$[H_3SO_4^+][HSO_4^-] = K_1 \qquad (35)$$

because activity coefficients are constant and the activity of the solvent does not vary greatly. As the addition of water pro-

[36] Lichty, *J. Am. Chem. Soc.*, **30**, 1834 (1908).

duces bisulfate ions by virtue of reaction (IX), it must decrease the concentration of $H_3SO_4^+$ if equation (35) is to hold, and the consequent repression of the solvent ionization decreases the concentration of HSO_4^- as well as that of $H_3SO_4^+$. If a is the concentration of $H_3SO_4^+$ or of HSO_4^- in the pure acid, c the stoichiometric concentration of water, and $a - x$ the concentration of $H_3SO_4^+$ after the addition of the water, the total ion concentration of the solution is $2c + 2(a - x)$, and the increase over the value in the pure solvent is $2(c - x)$; c moles of water yield, therefore, less than $2c$ moles of ions. Since x cannot be greater than a, it becomes negligible in comparison with c when $c \gg a$; consequently, at high concentrations of water each mole of water yields practically two moles of ions, and the freezing-point plot becomes linear with a slope twice the value of the cryoscopic constant.

The sulfur trioxide dissociation of the solvent complicates the quantitative treatment but does not alter the qualitative effect. Since water is converted into oxonium ion, the process must be written

$$2H_2SO_4 \rightleftharpoons SO_3 + OH_3^+ + HSO_4^- \qquad \text{(XVII)}$$
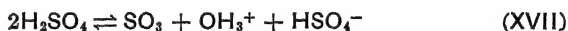
with some ionization process for the SO_3, probably

$$SO_3 + 2H_2SO_4 \rightleftharpoons H_3SO_4^+ + HS_2O_7^- \qquad \text{(XVIII)}$$
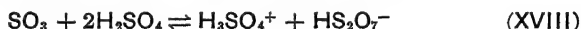
superposed. Since reaction (XVII) produces oxonium and bisulfate ions, it must also be repressed by the addition of water the ionization of which yields the same ions.

If some other base than water, such as $NaHSO_4$ which consists of sodium ions and bisulfate ions or ammonia which reacts to form ammonium ions and bisulfate ions, is added, the solvent dissociation will again be repressed and the increase in solute concentration will again be less than two moles per mole of base. But if the base is added to sulfuric acid that already contains enough water to make x nearly as great as a, the further repression produces no significant change in solute concentration, and the molar freezing-point depression will be twice that of a nonelectrolyte. The complications due to the ionization of the solvent may, therefore, be completely eliminated by using sulfuric acid containing a small amount of water instead of pure

sulfuric acid as the solvent for the cryoscopic investigation of bases.

From the thermodynamic equation

$$\frac{a_{\text{H}^+} a_{\text{HSO}_4^-}}{a_{\text{H}_2\text{SO}_4}} = K_2 \tag{36}$$

and the definition of H_0, it follows that

$$H_0 = -\log \frac{a_{\text{H}_2\text{SO}_4} f_{\text{B}}}{a_{\text{HSO}_4^-} f_{\text{BH}^+}} \tag{37}$$

and since activity coefficients and the activity of the solvent are effectively constant in dilute solutions

$$H_0 = \log [\text{HSO}_4^-] + c_1 \tag{38}$$

with c_1 a constant. From equation (35) it follows further that

$$H_0 = -\log [\text{H}_3\text{SO}_4^+] + c_2 \tag{39}$$

Equations (38) and (39) relate H_0 to the characteristic lyate- and lyonium-ion concentrations of the solvent in the same way that the equations $\text{pH} = \log [\text{OH}^-] + 14$ and $\text{pH} = -\log [\text{OH}_3^+]$ do with the pH in water.

Since $\log k$ in the formic acid decomposition is linear in H_0 with a slope of -1, equations (38) and (39) imply that for this reaction

$$\left. \begin{array}{c} \log k = -\log [\text{HSO}_4^-] + c_3 = \log [\text{H}_3\text{SO}_4^+] + c_4 \\ \text{or} \\ k = \dfrac{k_1}{[\text{HSO}_4^-]} = k_2 [\text{H}_3\text{SO}_4^+] \end{array} \right\} \tag{40}$$

The rate is, therefore, proportional to the concentration of the lyonium ion and inversely proportional to that of the lyate ion, just as the rate of an acid-catalyzed reaction in aqueous solution varies directly with the concentration of oxonium ion and inversely with that of hydroxyl ion.

Inhibition by Other Bases Than Water.—The effect of other bases than water has been extensively investigated in the closely related decomposition of malic acid, in which carbon monoxide is likewise produced from the carboxyl group and for which k is likewise proportional to h_0 in dilute solutions of the solute water. In Fig. 9 the specific rate at $40°$ (in unknown units)

is plotted against the stoichiometric concentration of added base for the bases water, sodium, potassium and silver bisulfates, dimethylpyrone, and acetic acid.[37] Each of these yields one mole of bisulfate ion per mole of base; the solutions contain in addition the bisulfate ion that results from the solvent ionization; hence the plot is not linear. Except for those referring to acetic acid, the divergence of which may be due to its interaction with the hydroxyl group of the malic acid, the points all lie on a single

⊕ H_2O	◓ Dimethylpyrone
◔ $KHSO_4$	◐ $Ag HSO_4$
○ Acetic acid	○ $Na HSO_4$
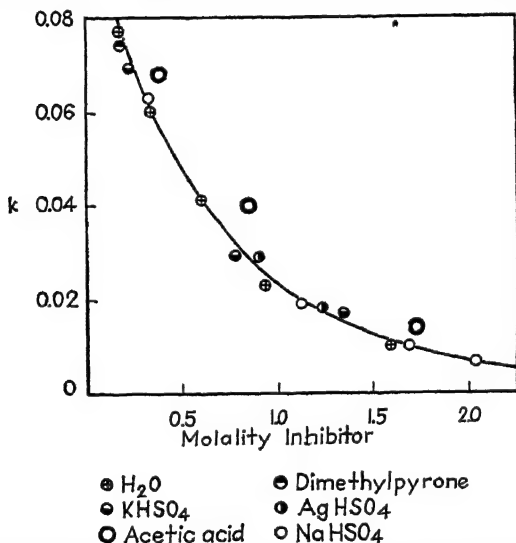
Fig. IX-9.—Effect of bases on the specific rate of the malic acid decomposition.

curve. This demonstrates that the rate is, in fact, an inverse function of the bisulfate-ion concentration.

The effect of a large number of other solutes upon the same reaction has been investigated[38] at the two concentrations 0.25M and 0.5M. At 30° the specific rate (in unknown units) in pure sulfuric acid is 0.0471. The following substances, present in 0.5M concentration, reduce this to the value given: benzophenone, 0.0133; benzoic acid, 0.0141; acetophenone, 0.0158. These bases are known (page 47) to yield one mole of bisulfate ion per mole of base; the rates are, therefore, nearly identical. The following

[37] WHITFORD, *J. Am. Chem. Soc.*, **47**, 953 (1925).

[38] DITTMAR, *J. Am. Chem. Soc.*, **52**, 2746 (1930).

substances, known to yield two moles of bisulfate ion per mole of base, have the same effect at 0.25M as the others do at 0.5M, *viz.*: ammonium sulfate, 0.0139; triphenylcarbinol, 0.0166. To judge by the kinetic data, crotonic, *o*-toluic, and phosphoric acids yield one mole of bisulfate ion per mole of base; phenol and *p*-cresol, between one and two; ethyl alcohol and *m*-nitrophenol, less than one; benzoic anhydride, which reduces the rate to a very low value, probably esterifies the hydroxyl group in the malic acid.

Mechanism of the Acid Decompositions.—It is reasonable that these reactions should show an acid catalysis. Whatever their detailed mechanism, they necessarily involve the separation of the group attached to the carboxyl in the form of a positive ion. This is most easily appreciated in the case of triphenylacetic acid, the decomposition of which

$$(C_6H_5)_3C - CO_2H + 2H_2SO_4 \rightarrow (C_6H_5)_3C^+ + OH_3^+ + 2HSO_4^- + CO \quad (XIX)$$
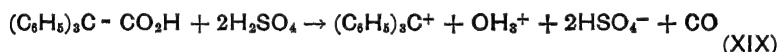
yields an ion stable in the medium, but it is inevitably true in all similar reactions. Such a rupture must be facilitated by the accumulation of protons on the carboxyl group, and this is a sufficient condition for an acid catalysis.

Formic acid is probably not significantly ionized in sulfuric acid because the specific rate of its decomposition drops off with time in pure sulfuric acid. Were the formic acid ionized, the decomposition

$$HC(OH)_2^+ \rightarrow OH_3^+ + CO \quad (XX)$$

would not alter the acidity of the medium and the specific rate would be unchanged. If the mechanism is

$$[HCO]^+ + H_2SO_4 \rightarrow CO + H_3SO_4^+ \quad (XXIII)$$
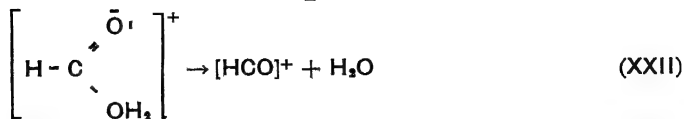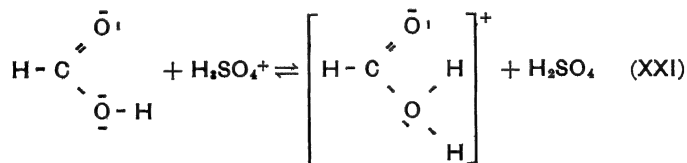
with either reaction (XXI) or (XXII) rate determining, the observed relation between rate and acidity follows.

In the analogous decomposition of oxalic acid[39] the plot of log k against H_0 shows a slope of -2 as the following data indicate:

% H_2O........	0.60	0.70	0.80	1.00	1.20	1.50	2.00	3.00
log k..........	-1.74	-1.88	-1.99	-2.17	-2.31	-2.50	-2.70	-3.23
$-(2H_0 + \log k)$	20.76	20.72	20.75	20.75	20.71	20.74	20.68	20.67

Such a relationship can be accounted for by the reversible addition of one proton to form (B) followed by the rate-deter-

(B)   (C)
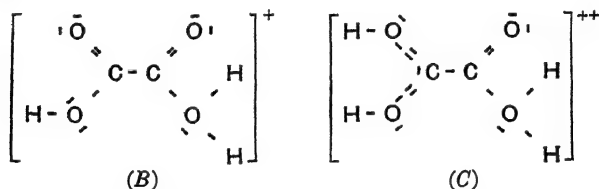
mining addition of a second proton to form (C) and a rapid breakdown into fragments which are finally converted to CO_2 and CO.

The decomposition of citric acid[40] to form acetonedicarboxylic acid and carbon monoxide also shows a slope of -2 in the log $k - H_0$ plot over a considerable range, but the rate goes through a maximum in the region of 99.5 per cent H_2SO_4 instead of increasing steadily. Such maxima have also been observed in acid-catalyzed reactions in aqueous solution and imply merely that the rate-determining step involves a substance or a group of substances whose concentration or the product of whose concentrations goes through a maximum in the solution of maximum rate. Thus a reaction the rate of which is proportional to the concentration of the acid oxalate ion $HC_2O_4^-$ must show a maximum rate in a solution that is neither so acid that the $HC_2O_4^-$ is converted largely to $H_2C_2O_4$ nor so basic that it is converted largely to $C_2O_4^-$. Given 14 unshared electron pairs in citric acid, each of which might conceivably add a proton, the appearance of the maximum in its reaction rate is not surprising. The

[39] Lichty and Bredig, *Z. Elektrochem.*, **12**, 459 (1906). Lichty, *J. Phys. Chem.*, **11**, 225 (1907).

[40] Wiig, *J. Am. Chem. Soc.*, **52**, 4729 (1930).

decomposition of triphenylacetic acid shows a slope of 3, which implies a third-order dependence of rate on acidity. There can be little doubt that nitration and the many other reactions for which sulfuric acid is the standard condensing agent are acid catalyzed in the same sense as these decompositions, but kinetic data for their interpretation are still lacking.

Acid and Base Catalysis of Acetylation Reactions.—The behavior of acetylation reactions in an acetic acid solvent offers a striking example of the utility of the concept of acid and base
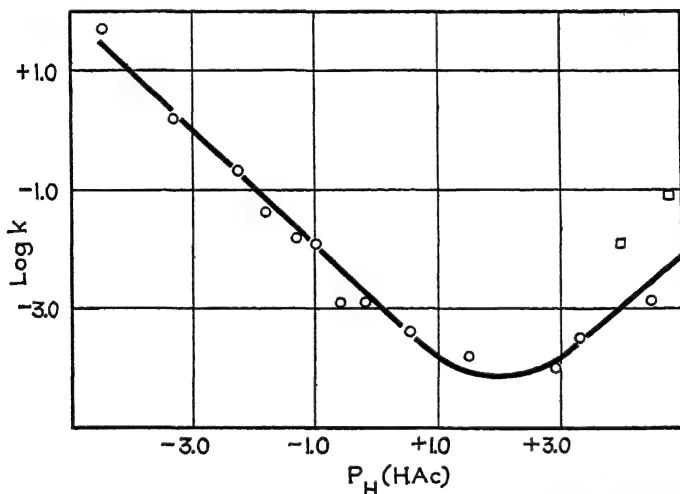
Fig. IX-10.—Comparison of the specific rate k of the acetylation of β-naphthol in acetic acid with the electrometrically determined acidity $P_H(HAc)$.[41]

catalysis in nonaqueous solutions. It has long been known that acetic anhydride is a relatively unreactive reagent by itself and that a "condensing agent" must be used, such diverse substances as sulfuric acid, sodium acetate, and tertiary amines being recommended. A kinetic study of the reaction[41] has led to the relationship between the specific rate of the acetylation of β-naphthol by acetic anhydride in acetic acid and an electrometrically determined acidity which is shown in Fig. 10. The points on the left branch of the curve at high acidities were obtained by using such strong acids as perchloric, sulfuric, and

[41] CONANT and BRAMANN, *J. Am. Chem. Soc.*, **50**, 2305 (1928).

naphthalenesulfonic or buffer solutions of these with weak bases. Since they lie on a single straight line of unit slope in the logarithmic plot, the reaction appears to follow a specific lyonium-ion catalysis, *i.e.*, a catalysis by the solvated proton, $CH_3C(OH)_2^+$. As the acidity decreases, the rate goes through a minimum and rises again, showing the presence of a basic catalysis. The points due to pyridine (squares) lie higher than those due to sodium or potassium acetate (circles); consequently, a general basic catalysis is indicated.

The phenomenon of a minimum rate at a definite pH with catalysis both by acids and by bases is a familiar one in aqueous solutions, and the plot of Fig. 10 could be duplicated in most of its features in the hydrolysis of an ester, the bromination of a ketone, or the mutarotation of glucose.

The acetylation of cellulose is catalyzed by acids in proportion to their inherent acid strength. Thus HCl and H_3PO_4 are much poorer catalysts than $HClO_4$, H_2SO_4, and HI.[42] The unexpected fact that mixtures of H_3PO_4, HCl, or $ZnCl_2$ with $NaClO_4$ are much better catalysts than either component alone can be accounted for if molecular $HClO_4$ is a very powerful catalyst in agreement with its great inherent acidity.

Acid Catalysis in Aniline and Related Solvents.—The work of Goldschmidt in aniline and related solvents, begun in 1899,[43] foreshadowed many of the present conclusions of acid-base theory. Using the rate of the diazoamino rearrangement (page 325) as a measure of acidity, he found it proportional to the concentration of acid, *i.e.*, to the concentration of anilinium ion formed from the acid. The catalytic constants times 10^5 at 45° in *p*-toluidine are as follows: HBr, 4.69; HCl, 2.94; picric acid, 6.1; *o*-nitrobenzoic acid, 0.483; *m*-nitrobenzoic acid, 0.172; *p*-nitrobenzoic acid, 0.169. Similar results are obtained with solutions in aniline and in *m*-chloraniline, the rates being about an order of magnitude greater in aniline and considerably greater yet in *m*-chloraniline. This is in the order of the acid strengths of the conjugate acids of these bases. The conductivity of acids in these solvents bears no relation to the magnitude of the

[42] Krüger and Roman, *Angew. Chem.*, **47**, 58 (1934).
[43] Reviewed in Goldschmidt, *Z. Elektrochem.*, **36**, 662 (1930).

catalytic constant, a common phenomenon in solvents of low dielectric constant.

Bromide ion added as the salt $C_6H_5N(CH_3)_3^+ + Br^-$ has little effect on the rate in aniline or in p-toluidine but decreases it 50 per cent when one mole of salt is added to one mole of HBr in m-chloraniline. It appears, therefore, that HBr is a strong acid, *i.e.*, the reaction

$$HBr + C_6H_5NH_2 \rightleftharpoons C_6H_5NH_3^+ + Br^- \qquad (XXIV)$$
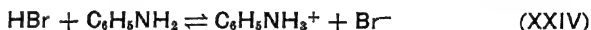
is effectively complete, in the first two solvents, but is incompletely ionized in the less basic chlorine derivative.

Moderately strong bases decrease the rate of the HBr catalyzed reaction, and the basicity constant

$$K_b^c = \frac{[BH^+]}{[B][C_6H_5NH_3^+]} \qquad (41)$$

may be calculated from the decrease in rate. The value of K_b^c thus calculated is nearly independent of the concentrations of HBr and of base, and the same value is obtained with other acids than HBr. For a series of 12 aliphatic tertiary amines and pyridine derivatives the values of K_b^c parallel the basicity constants in water K_b^w, the equation

$$\log K_b^c = -3.78 + 0.83 \log K_b^w \qquad (42)$$

being satisfied with a median deviation of 0.18 and a range of 6 units in $\log K_b^w$.

Acid and Base Catalysis in Other Amphiprotic Solvents.—The nitramide decomposition in m-cresol shows a general base catalysis, and the catalytic constants are related to the base strengths of catalysts of related structure by the Brønsted law.[44] Base strengths in this solvent deviate considerably from exact parallelism with the strengths of the same bases in water, and the parallelism between rate and base strength is much closer when the base strengths measured in cresol are used than it is with the strengths measured in water. The nitramide catalysis has also been studied in i-amyl alcohol, and the catalytic constants show

[44] BRØNSTED, NICHOLSON, and DELBANCO, *Z. physik. Chem.*, **A169**, 379 (1934).

a parallelism to the base strengths in water, those in i-amyl alcohol being unknown.[45]

Catalysis in Aprotic Solvents.—Catalysis in a solvent that is of negligible acidity and basicity, a so-called aprotic solvent, is necessarily of the general type, for no appreciable concentrations of either lyonium or lyate ions are present. In this sense the phenomena are simpler than in solvents in which the solvent molecules are both acid and base, and are converted by other acids and bases to the lyonium and lyate ions. Against this advantage are the many disadvantages that cluster around the investigation of ionic reactions in a medium of low dielectric constant.

The diazoacetic ester decomposition has been used for many years for the determination of oxonium-ion concentration in aqueous solution and is a specific oxonium-ion catalysis in water.[46] The chief reaction under these conditions is the formation of glycollic acid

$$C_2H_5OOC.CHN_2 + H_2O \rightarrow C_2H_5OOCCH_2OH + N_2 \qquad (XXV)$$

which follows the rate law

$$v = k_1[\text{ester}][OH_3^+] \qquad (43)$$

In the presence of halide or nitrate ions it is accompanied by such reactions as

$$C_2H_5OOCCHN_2 + HCl \rightarrow C_2H_5OOCCH_2Cl + N_2 \qquad (XXVI)$$
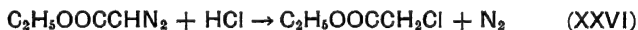
which follow the rate law

$$v = k_2[\text{ester}][OH_3^+][Cl^-] \qquad (44)$$

A plausible mechanism involves the reversible addition of the proton

$$C_2H_5OOCCHN_2 + OH_3^+ \rightleftharpoons C_2H_5OOCCH_2N_2^+ + H_2O \qquad (XXVII)$$
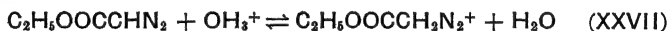
after which glycollic and halogen or nitratoacetic ester are formed by competition between the reactions

$$C_2H_5OOCCH_2N_2^+ + H_2O \rightarrow [C_2H_5OOCCH_2OH_2]^+ + N_2 \qquad (XXVIII)$$
$$C_2H_5OOCCH_2N_2^+ + Cl^- \rightarrow C_2H_5OOCCH_2Cl + N_2 \qquad (XXIX)$$
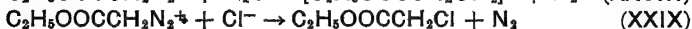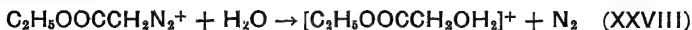
[45] BRØNSTED and VANCE, *Z. physik. Chem.*, **A163**, 240 (1932).
[46] BREDIG and RIPLEY, *Ber.*, **40**, 4015 (1907). BRØNSTED and DUUS, *Z. physik. Chem.*, **117**, 299 (1925).

It is, therefore, not surprising to find that in the solvent benzene[47] the reaction of diazoacetic ester with the halogen acetic acids or with formic or picric acid is approximately second order in the acid. One molecule plays the part of the oxonium ion in reaction (XXVII), the other reacts with the ion thus formed in the same way as the water in equation (XXVIII). The situation is complicated by the known fact that most of these acids are largely associated to a dimeric form in this solvent; the order of the reaction, somewhat less than 2, may perhaps result from a partial dissociation of the dimer to a more reactive monomer. The addition of a small concentration of phenol considerably increases the rate of nitrogen evolution, presumably by way of a new fast reaction to form phenoxyacetic ester. The rate is proportional both to the concentration of the phenol and to that of the catalyzing acid. The catalytic constants for the reaction with phenol satisfy the Brønsted law with moderate precision when the acid strengths that obtain in aqueous solution are used in default of those in benzene (page 290).

The rates of reaction of di-p-tolyldiazomethane with various derivatives of benzoic acid in benzene is first order in diazo compound and first order in the acid. They are approximately in the order of the acid strengths.[48]

Important studies on acid catalysis in aprotic solvents, especially in chlorobenzene, have been carried out with the rearrangement of N-bromacetanilide, the depolymerization of paraldehyde, the inversion of l-menthone, and the racemization of C_6H_5CO—$CH(CH_3)$—C_6H_5 and of C_6H_5CO—$CH(CH_3)$—C_2H_5.[49] The reactions are in no case of integral order. With respect to the substrate the order is somewhat less than unity in every case except the paraldehyde reaction in which it is unity. This can be interpreted as the result of complex formation of the hydrogen bonding type between substrate and acid if the complex is unreactive. There is direct evidence in the menthone

[47] Brønsted and Bell, *J. Am. Chem. Soc.*, **53**, 2478 (1931).

[48] Norris and Strain, *J. Am. Chem. Soc.*, **57**, 187 (1935).

[49] Bell, *Proc. Roy. Soc.* (London), **A143**, 377 (1934). Bell and Levinge, *ibid.*, **A151**, 211 (1935). Bell, Lidwell, and Vaughan-Jackson, *J. Chem. Soc.*, 1792 (1936). Bell and Caldin, *ibid.*, 382 (1938). Bell, Lidwell, and Wright, *ibid.*, 1861 (1938).

case for the rapid and reversible formation of complexes of menthone and acid in the effect of acids on the optical rotation of the menthone solution.

The dependence of the specific rate k on acid concentration c may be expressed in the case of weaker acids by

$$k = k_A c + a\sqrt{c} \qquad (45)$$

in the case of stronger acids by

$$k = k_A c + bc^2 \qquad (46)$$

The latter equation also fits the diazoacetic ester reaction. In the paraldehyde reaction the order is between 1.5 and 2.5 with respect to the acid concentration.

The fractional orders may be attributed to complex formation between substrate and acid; to the necessity of two molecules reacting, one as acid, the other as base; or to the usual difficulty of interpreting electrochemical phenomena in solvents of this type.

TABLE VI.—GENERAL ACID CATALYSIS IN APROTIC SOLVENTS[49]

Reaction, medium, temperature	n	r	x
Diazoacetic ester + phenol, benzene, 15°..............	6	0.16	1.0
Bromacetanilide, chlorbenzene, 15°...................	8	0.01	0.30
Paraldehyde, anisole, 100.5°.........................	3	0.12	1.2
Menthone, chlorbenzene, 99.4°.......................	6	0.06	0.55
Phenylmethylacetophenone, chlorbenzene, 99.4°........	4	0.13	0.80

The catalytic constants k_A given by equation (45) or (46) satisfy the Brønsted catalysis law with reasonable precision when acid strengths measured in water are applied, provided that carboxylic acids only are involved. The point for picric acid deviates widely. Data on the carboxylic acids are given in Table VI, x being the slope, r the probable error, and n the number of acids. The specific rate of the paraldehyde reaction varies in the ratio 328:11.5:0.35 among nitrobenzene, benzene, and anisole solutions; the other reactions run at about the same rates in anisole, nitrobenzene, chlorbenzene, decalin and the like.

CHAPTER X

CARBONIUM-ION REACTIONS

On the Methods of Preparative Organic Chemistry.—The molecule of the typical carbon compound is a stable structure surrounded by electrical fields which are most effective walls of defense against reaction. The problem of the synthetic chemist has been therefore to discover the weak points in the walls and to develop powerful agents of attack, which shall nevertheless not be so violent as to bring the whole structure to ruins. To a remarkable extent the resulting tactics fall into three groups. In one of these, the *carbonium-ion reactions*, a carbonium ion is either formed as an intermediate or transferred, without being set free, from one linkage to another. In a second group, the *carbonyl-addition reactions*, a nucleophilic reagent is added to the carbon of a carbonyl or similar group. In the third, the *radical reactions*, the attacking reagent is an atom or a free radical.

The Sources of Carbonium Ions: Alkyl Halides, Etc.—The common feature of all carbonium-ion reactions is the linking of a carbonium ion to a nucleophilic reagent; the source of the carbonium ion and the nature of the driving force that sets it free or loosens its previous linkage so that it is easily transferred to a new one differ from case to case. When the carbonium carbon is initially attached to a weakly nucleophilic group, as it is in alkyl halides, toluenesulfonates, and sulfates, in quaternary ammonium ions, and in the conjugate acids of alcohols (ROH_2^+) and the like, the carbonium-ion type of reaction may occur by direct transfer to a nucleophilic reagent. These are the nucleophilic displacements on carbon (page 143), and the driving force is the affinity of the unshared electron pairs of the reagent for the carbonium ion. The same reactions may be initiated by the attack of an electrophilic reagent, *i.e.*, by the action of mercuric or silver salts or of aluminum chloride on alkyl halides (page 138); by the action of strong acids or of boron fluoride or aluminum

chloride on alcohols and other oxygen compounds (page 140); by the action of solvent molecules in the solvolytic process (page 167); in fact, by the action of any sufficiently active electrophilic reagent on a carbon compound that contains unshared electron pairs. In this case it is convenient to refer to the carbonium ion as being set free as an unstable reaction intermediate, but its freedom is apparently never complete (page 171). The reactions that depend upon an electrophilic attack may be differentiated from the nucleophilic displacements by the nature of the reagents used, by the effect of changing structure of the alkyl group (page 169), and by the extent to which racemization (page 170) or rearrangement (page 315) of the carbonium ion occurs.

Carbonium Ions from Olefins.—Altogether the most satisfactory explanation of the complex set of reactions, involving hydration, the formation of sulfuric esters, condensations, polymerization, and rearrangement, which accompany the solution of an olefin in strong sulfuric acid, is in terms of a carbonium-ion intermediate.[1] With the more reactive olefins the hydration may be studied kinetically in dilute aqueous acids.[2] The hydration of trimethylethylene, of *as*-methylethylethylene, and of crotonaldehyde are second-order reactions of olefin with acid. The specific rates for various strong acids are nearly the same; in the case of trimethylethylene at 25° in 0.1M acid solution they are as follows: HCl, 2.52×10^{-4}; $HClO_4$, 2.37×10^{-4}; HBr, 2.34×10^{-4}; HNO_3, 2.25×10^{-4}; $C_7H_7SO_3H$, 2.03×10^{-4}. The addition of 0.9M KNO_3 increases the rate to 3.73×10^{-4}, indicating a relatively large salt effect. In mixtures of HNO_3 and KNO_3 of constant ionic strength the rate is strictly proportional to the concentration of the acid. In view of this and the similarity of the effects of the different strong acids, the actual reactant must be oxonium ion and the mechanism

$$\underset{\substack{|\\CH_3}}{CH_3-C}\!=\!\!\underset{\substack{|\\H}}{C}-CH_3 + OH_3^+ \rightleftharpoons \left[\underset{\substack{|\\CH_3}}{CH_3-C}\!-\!\!\underset{\substack{|\\H}}{\underset{\substack{|\\H}}{C}}-CH_3 \right]^+ + H_2O \quad (I)$$
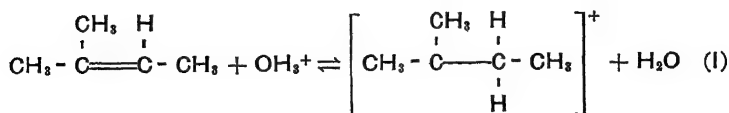
[1] WHITMORE, *Ind. Eng. Chem.*, **26**, 94 (1934).

[2] LUCAS and EBERZ, *J. Am. Chem. Soc.*, **56**, 460 (1934). LUCAS and YUI, *ibid.*, **56**, 2138 (1934). WEINSTEIN and LUCAS, *ibid.*, **59**, 1461 (1937).

$$\left[\begin{array}{c} CH_3\ H \\ CH_3 - C{\rule{1.2cm}{0.4pt}}C - CH_3 \\ H \end{array}\right]^+ + H_2O \rightarrow \left[\begin{array}{c} CH_3\ H \\ CH_3 - C{\rule{1.2cm}{0.4pt}}C - CH_3 \\ H - O \quad H \\ H \end{array}\right]^+ \qquad (II)$$
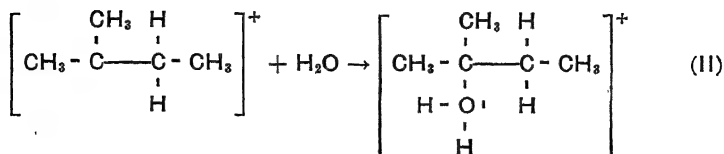
The product of reaction (II) is the conjugate acid of the alcohol and is in mobile equilibrium with it. The catalysis is of the specific oxonium-ion type; the observed first-order constant in a 0.105M solution of acetic acid being 0.30×10^{-6}, whereas that calculated for the oxonium-ion reaction is 0.28×10^{-6}. For 0.101M oxalic acid the corresponding values are 1.2×10^{-6} and 1.0×10^{-6}. A specific oxonium-ion catalysis leaves the question of the rate-determining step open.

The reaction is favored by the accumulation of alkyl groups on one unsaturated carbon of the olefin since hydration in dilute aqueous acids is observed only when two such alkyl groups are present. It is hindered by alkyl groups on the other olefin carbon since $(CH_3)_2C{=}CHCH_3$ hydrates at a rate 60 per cent less than that of $(CH_3)_2C{=}CH_2$. The easy hydration of crotonaldehyde depends upon the conjugation that brings into play the relatively high basicity of the oxygen atom, the intermediate being (A). The slow hydration of allyl alcohol and of crotonic

$$\left[\begin{array}{c} H_3C - C {\cdots} C {\cdots} C {\cdots} \bar{O} - H \\ H \quad H \quad H \end{array}\right]^+ \qquad \left[\begin{array}{c} \bar{O} - H \\ H_3C - C = C - C \\ H \quad H \quad \bar{O} - H \end{array}\right]^+$$
$$(A) \hspace{4cm} (B)$$
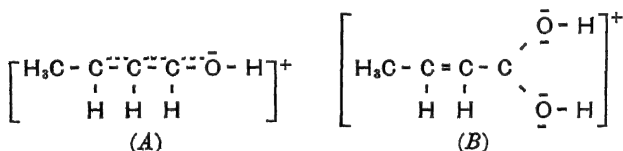
acid is intelligible since conjugation is lacking in the first and the predominant resonating form in the conjugate acid of the second is (B).

There is independent evidence that unsaturated hydrocarbons possess the proton affinity which equation (I) implies in the fact that they dissolve in liquid hydrofluoric acid, whereas saturated hydrocarbons do not.[3] Olefins polymerize to high molecular weight substances of low solubility, a reaction that itself probably goes by way of a proton addition (page 307)

[3] KLATT, *Z. anorg. allgem. Chem.*, **234**, 189 (1937).

but aromatic hydrocarbons dissolve without such complications and may be recovered unchanged. The solubilities of benzene, toluene, anthracene, *m*- and *o*-xylene, and tetrahydronaphthalene range from 0.23 to 3.11 per cent at 0°C. The solutions are colored, and the rate of solution is far from instantaneous. Electrophilic reagents like $Hg(CN)_2$, $Hg(N_3)_2$, AgN_3, AgF, and TlF increase the solubility of the hydrocarbon and are themselves more soluble in its presence, which indicates that they displace the equilibrium between hydrocarbon and HF

$$C_6H_6 + HF \rightleftharpoons C_6H_7^+ + F^- \tag{III}$$
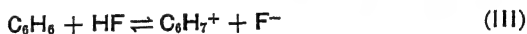
by combining with fluoride ion, *e.g.*,

$$Hg^{++} + 4F^- \rightleftharpoons HgF_4^- \tag{IV}$$

The two reactions are thus mutually helpful.

Diazotization. — The first unambiguously known product of the action of nitrous acid on amines is the diazonium ion. The kinetics have been thoroughly investigated in the case of aniline;[4] the rate law in aqueous sulfuric acid being

$$v = \frac{k_1[C_6H_5NH_3^+][HNO_2]^2}{K_b[OH_3^+]} = k_1[C_6H_5NH_2][HNO_2]^2 \tag{1}$$

and that in hydrochloric acid shows an additional reaction which makes the complete equation

$$v = [C_6H_5NH_2]\{k_1[HNO_2]^2 + k_2[HNO_2][OH_3^+][Cl^-]\} \tag{2}$$

These kinetics may be accounted for if the rate-determining steps involve aniline base and either N_2O_3 or NOCl formed by the mobile and reversible reactions[5]

$$2HNO_2 \rightleftharpoons N_2O_3 + H_2O \tag{V}$$
$$HNO_2 + OH_3^+ + Cl^- \rightleftharpoons NOCl + 2H_2O \tag{VI}$$

All nitrous acid derivatives contain, at least in one resonance form, a nitrogen atom carrying only six electrons, which, together with the unshared pair on the aniline nitrogen, is the probable source of the nitrogen-nitrogen link in the diazonium ion, thus

[4] Schmid and Muhr, *Ber.*, **70B**, 421 (1937).

[5] Abel, Schmid, and Weiss, *Z. physik. Chem.*, **A147**, 69 (1930).

$$C_6H_5 - \overset{\overset{\text{H}}{|}}{\underset{\underset{\text{H}}{|}}{N}} \cdot + \underset{\underset{\text{$\cdot$O$\cdot$}}{|}}{\bar{N}} - \bar{\underline{O}} - \underline{N} = \bar{O} \cdot \rightarrow C_6H_5 - \overset{\overset{\text{H}}{|}}{\underset{\underset{\text{H}}{|}}{N}} - \underset{\underset{\text{$\cdot$O$\cdot$}}{|}}{\bar{N}} - \bar{\underline{O}} - \underline{N} = \underline{O} \cdot \qquad \text{(VII)}$$
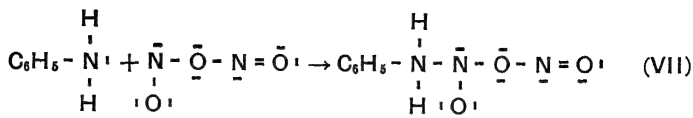
The loss of a water molecule and a nitrite ion will then lead to the diazonium ion.

The diazonium ion reacts reversibly in water

$$[C_6H_5 - N \equiv N \cdot]^+ + [\cdot \bar{\underline{O}} - H]^- \rightleftharpoons C_6H_5 - \bar{N} = \bar{N} - \bar{\underline{O}} - H \qquad \text{(VIII)}$$
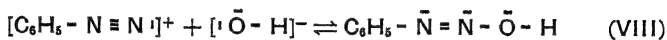
to form a compound that exists in stereoisomeric forms and carries a weakly acidic proton. By virtue of the latter property it is converted in strongly alkaline media to diazotate ion

$$[C_6H_5 - \bar{N} = \bar{N} - \bar{\underline{O}} \cdot]^-.$$
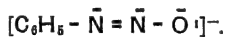
The Reactions of Diazonium Ions.—Many of the characteristic reactions of aromatic diazonium salts may be interpreted either as nucleophilic displacements of the type

$$[H - \bar{\underline{O}} \cdot]^- + [R - N \equiv N \cdot]^+ \rightarrow H - \bar{\underline{O}} - R + \cdot N \equiv N \cdot \qquad \text{(IX)}$$
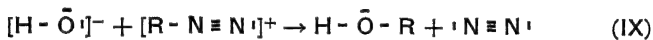
or as the result of a spontaneous formation of a carbonium ion

$$[R - N \equiv N \cdot]^+ \rightarrow R^+ + \cdot N \equiv N \cdot \qquad \text{(X)}$$

followed by its further reaction. Other reactions suggest the intermediate formation of free radicals (page 383). The characteristic effect of cuprous compounds in the Sandmeyer reaction has no obvious explanation.

The Nitrous Acid-amine Reaction.—Glycine reacts with nitrous acid according to the same kinetics as those of the diazotization,[6] but the first isolable product is glycollic acid. It is of course highly probable that the reaction goes by way of the diazonium ion which decomposes according to reaction (IX) or (X). In many reactions of this sort, rearrangement phenomena occur which indicate the transient formation of a free carbonium ion and favor reaction (X) over reaction (IX) (page 315). Thus *n*-propylamine yields *i*-propyl alcohol when treated with nitrous acid.

[6] ABEL, SCHMID, and SIDON, *Z. Elektrochem.*, **39**, 863 (1933).

Even the decomposition of ammonium nitrite to form nitrogen and water follows a similar kinetics[7]

$$v = k[NH_3][HNO_2]^2 \qquad (XI)$$

and probably a similar course.

When an amine contains hydrogen attached to the α-carbon, the action of nitrous acid often leads to an isolable diazo compound. These presumably result from the reaction

$$\begin{bmatrix} R \\ \diagdown \\ \diagup \quad CH - N \equiv N \text{'} \\ R \end{bmatrix}^+ + B \rightleftharpoons \begin{array}{c} R \\ \diagdown \\ \diagup \\ R \end{array} C = N = \overset{..}{\underset{..}{N}} + BH^+ \qquad (XII)$$
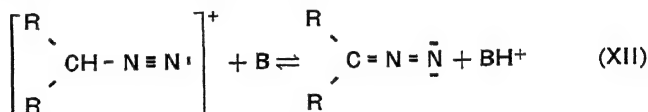
This reaction in the reverse direction is probably the first step in the acid-catalyzed decomposition of diazoacetic ester (page 288).

Reactions of Carbonium Ions.—When a carbonium ion is set free or when the linkages that bind it have been greatly weakened by one of the processes just considered, a great variety of reactions is possible. The ion may attach itself to a base, *i.e.*, to any substance carrying an unshared electron pair. When the base is hydroxyl ion or water, the product is an alcohol or its conjugate acid; when the base is alcoholate ion or alcohol, the product is an ether or its conjugate acid; with chloride, nitrate, or acetate ions, esters are formed; with ammonia or amines, substituted ammonium ions are formed.

When the base is a carbanion, a new carbon-carbon linkage results, and many familiar chain-lengthening procedures depend upon this reaction. The necessary carbanion may be obtained by the action of a base on a substance containing acidic protons. Thus sodium alcoholate in alcohol, sodium metal in benzene, even concentrated aqueous potassium hydroxide (20 per cent)[8] convert such substances as acetacetic ester, malonic ester, nitroalkyls, and cyanacetic ester into conjugate bases, which react readily with alkyl halides, toluenesulfonates, and the like. The reaction is a nucleophilic displacement in which a carbonium ion is transferred from its attachment to halide ion to a new link

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[7] ABEL, SCHMID, and SCHAFRANIK, *Z. physik. Chem., Bodenstein Festband,* 510 (1931).

[8] KNUNYANTS, C. A., **32**, 2908 (1938).

involving the carbon of the carbanion (page 143). The effect of the structure of the alkyl group is the typical one for this kind of displacement (page 154); the effect of alkyls on the carbanion carbon is revealed by the fact that monoalkyl derivatives are so easily obtained. This shows either that the equilibrium

$$[CH_3COCHCO_2C_2H_5]^- + CH_3COCHRCO_2C_2H_5 \rightleftharpoons CH_3COCH_2CO_2C_2H_5 +$$
$$[CH_3COCRCO_2C_2H_5]^- \quad (XIII)$$

favors the substances on the left of the equation or that the displacement reaction is slower with the alkylated ion than with the parent compound.

The action of the Grignard reagent on an alkyl halide involves a similar displacement by the carbanion contained in the reagent (page 145). The Wurtz-Fittig reaction probably has the same reaction as its final step.

When the base with which the carbonium ion combines carries unshared pairs in more than one part of the molecule, the prediction of the reaction product offers an interesting problem. Thus the conjugate base of acetacetic ester has a relatively high electron density on carbon, but it also possesses unshared electrons on oxygen. In most of its reactions it forms predominantly a new linkage to carbon, as it does when it reacts with an alkyl halide; in the reaction with acyl halides, however, it links also by way of oxygen. The substance (*C*) reacts with bases to form an ion (*D*) which reacts with methyl iodide to yield (*E*)[9]
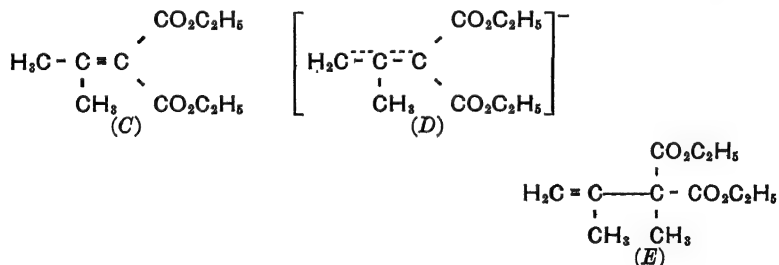
A similar situation did much to confuse the early development of the oxonium-salt theory. Dimethylpyrone (*F*) carries

[9] Kon and Speight, *J. Chem. Soc.*, 2727 (1926).

(F) (G)
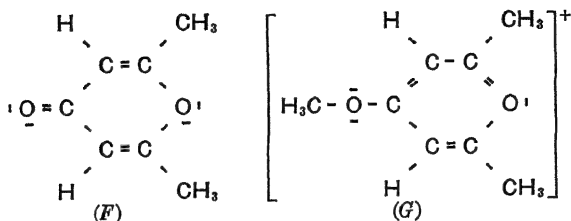
unshared pairs on both oxygen atoms; it reacts with methyl iodide exclusively to form (G).[10]

Cyanide and nitrite ions react with alkyl halides principally to form nitrile and nitrite

$$[\mathrm{I}\,C \equiv N\,\mathrm{I}]^- + R\text{-}X \rightarrow \mathrm{I} N \equiv C\text{-}R + X^- \qquad (XIV)$$

$$[\mathrm{I}\,\bar{O}\text{-}\underline{N}\text{-}\bar{O}\,\mathrm{I}]^- + R\text{-}X \rightarrow \mathrm{I}\,\bar{O} \equiv \underline{N}\text{-}\bar{O}\text{-}R + X^- \qquad (XV)$$
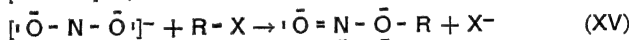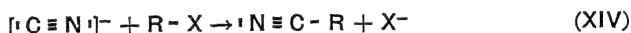
although amounts of isonitrile and nitrocompound varying with the nature of the alkyl group may also be formed, and chloracetic acid forms almost exclusively the nitrocompound (which decomposes to nitromethane). On the other hand, silver cyanide and nitrite, and probably the derivatives of other heavy metals, yield predominantly the isonitrile and the nitrocompound. This reaction appears to be due to the existence of a covalent link between silver and carbon in silver cyanide, which constrains the alkyl halide to react with the nitrogen

$$Ag\text{-}C \equiv N\,\mathrm{I} + R\text{-}X \rightarrow [Ag\text{-}C \equiv N\text{-}R]^+ + X^- \qquad (XVI)$$

$$[Ag\text{-}C \equiv N\text{-}R]^+ \rightarrow Ag^+ + \mathrm{I}\,C \equiv N\text{-}R \qquad (XVII)$$
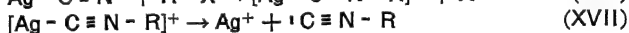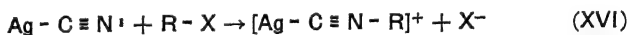
This picture is supported by the fact that the likewise covalently linked ferrocyanide ion can be alkylated to a product

$$Fe(CN)_6^{\blacksquare} + 6CH_3OSO_3CH_3 \rightarrow Fe(CNCH_3)_6^{++} + 6CH_3SO_4^- \quad (XVIII)$$
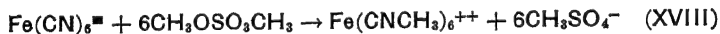
whose decomposition to isonitrile and reduction to methylamine demonstrate unambiguously that methyl is linked to nitrogen.[11]

The final product of a carbonium-ion reaction is very little affected by the source of the ion. One can get an alcohol, the product of the reaction of carbonium ion with water, by the hydrolysis of an alkyl chloride or sulfate, by the action of strong acid on an ether or an olefin, by the action of nitrous acid on an

[10] BAEYER, *Ber.*, **43**, 2337 (1910).

[11] HARTLEY, *J. Chem. Soc.*, **97**, 1725 (1910); **99**, 1549 (1911).

amine, by the acid-catalyzed decomposition of an aliphatic diazocompound, in fact, by carrying out in the presence of water any of the procedures calculated to yield a carbonium ion. The only limitation is that the base must not be too strong to be compatible with the acidity that may be necessary for the formation of the carbonium ion. One cannot alkylate ammonia with an olefin, because the high acidity necessary to convert the latter to the carbonium ion also transforms the ammonia into unreactive ammonium ion. One can, however, alkylate the weaker bases water and benzene with olefin and acid.

Many carbonium-ion reactions are reversible to an appreciable extent, and a desired reaction may fail because the reverse reaction is too fast rather than because the forward one is too slow. Such processes are uphill ones in the scale of free energies and are possible only if they are coupled with one that is downhill. Thus in the reaction of an alcohol with HCl, the uphill displacement of hydroxyl ion by chloride ion is accompanied by the downhill conversion of the hydroxyl ion to water, probably by the sequence

$$R - \overset{..}{\underset{..}{O}} - H + H - \overset{..}{\underset{..}{Cl}} \cdot \rightarrow \left[R - \overset{..}{\underset{\underset{H}{|}}{O}} - H \right]^{+} + [\cdot \overset{..}{\underset{..}{Cl}} \cdot]^{-} \rightarrow \cdot \overset{..}{\underset{..}{Cl}} - R + H - \overset{.}{\underset{..}{O}} \cdot H$$

$$(XIX)$$
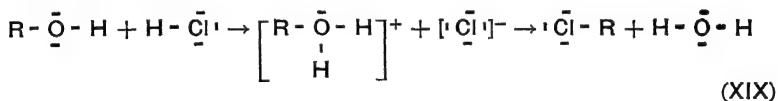
The same conversion may be achieved by reacting the alcohol with toluenesulfonyl chloride to form the alkyl toluenesulfonate. This reacts easily and completely with chloride ion

$$ROH + ClSO_2C_7H_7 \rightarrow ROSO_2C_7H_7 + HCl \qquad (XX)$$
$$ROSO_2C_7H_7 + Cl^- \rightarrow RCl + C_7H_7SO_3^- \qquad (XXI)$$
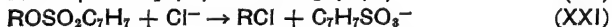
The reversal of the hydrolysis of an alkyl chloride is thus accomplished at the expense of the hydrolysis of the sulfonyl chloride. It is probable that the classical reagents phosphorus pentachloride and thionyl chloride convert alcohols to halides by a mechanism similar to that of equations (XX) and (XXI) and involving an intermediate of the type R—O—SO—Cl.

Etherification and Ether Hydrolysis.—From an alcohol one may obtain an ether, from an ether an alcohol by the action of acids or of other electrophilic reagents in what is obviously a carbonium-ion reaction. The classical formation of diethyl

ether from alcohol under the action of sulfuric acid can be duplicated by the action on alcohol of sulfonic acids, of boron fluoride, or of zinc chloride. Notable is the fact that hydrochloric acid leads to the formation of ether under conditions in which ethyl chloride reacts only negligibly with alcohol. Consequently, the reaction in this case does not go by way of ester formation from one molecule of alcohol followed by reaction of the ester with a second molecule. There is no good reason to suppose, therefore, that ethylsulfuric acid is the intermediate when sulfuric acid is the condensing agent.[12]

Table I indicates the wide range of reaction rates encountered in acid-catalyzed ether hydrolysis. The catalyst is a strong acid, usually benzenesulfonic, and the slower rates are extrapolated from measurements at 55 to 95° which lasted several months.

TABLE I.—CATALYTIC CONSTANTS FOR ACID-CATALYZED ETHER HYDROLYSIS AT 25°[13]

Substance	k	Substance	k
Diethyl ether	2.43×10^{-13}	Propylene oxide	0.00100
Ethyl i-propyl ether	2.50×10^{-12}	Furane	Very slow
Di-i-propyl ether	1.10×10^{-11}	α,α-Dimethylfurane	0.00027
Vinyl ethyl ether	2.9	Trioxymethylene	8.8×10^{-9}
Divinyl ether	0.0083	Formaldehyde dimeth-	
Ethylene oxide	0.0083	ylacetal	1.27×10^{-5}

The increase in rate produced by alkyl groups on the α-carbon (in isopropyl ethers) suggests a mechanism of the solvolytic type in which the conjugate acid of the ether reacts to form carbonium ion and alcohol, the former being almost immediately converted by a water molecule to the conjugate acid of the alcohol

$$\begin{bmatrix} R \\ \diagdown \\ \qquad \bar{O}-H \\ \diagup \\ R \end{bmatrix}^{+} \rightarrow R-\bar{O}-H + R^{+} \qquad \text{(XXII)}$$

$$R^{+} + H_2O \rightarrow \begin{bmatrix} \qquad\quad H \\ \qquad\diagup \\ R-\bar{O} \\ \qquad\diagdown \\ \qquad\quad H \end{bmatrix}^{+} \qquad \text{(XXIII)}$$
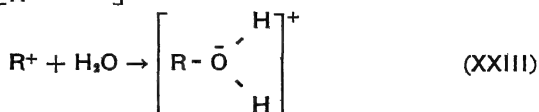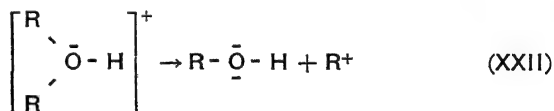
[12] VAN ALPHEN, *Rec. trav. chim.*, **49**, 754 (1930).
[13] SKRABAL and SKRABAL, *Z. physik. Chem.*, **181**, 449 (1938).

An even more marked acceleration is produced by the substitution of phenyl for hydrogen on the α-carbon. Benzhydrol is rapidly converted to its ethyl ether by heating with a dilute solution of HCl in ethanol, and similar treatment leads also to dibenzhydryl ether.[14]

The Reactions of Ethylene Oxides.—The internal ether ethylene oxide is an energy-rich and reactive substance because of its internal strain. A variety of reactions may occur in dilute aqueous solution.[15] There is first a slow uncatalyzed hydration to the glycol

$$H_2C\underset{O}{\overbrace{\hspace{1.2cm}}}CH_2 + H_2O \rightarrow H_2COH.CH_2OH \qquad (XXIV)$$
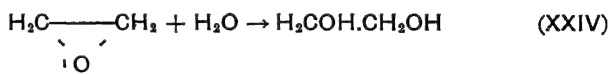
$$v_1 = k_1[S] \qquad S = \text{ethylene oxide} \qquad (3)$$

Perchloric acid, the conjugate base of which is very weakly nucleophilic, superimposes an acid-catalyzed hydration the rate of which is given by

$$v_2 = k_2[S][OH_3^+] \qquad (4)$$

With the halogen hydrides, with carboxylic acids and even with nitric and benzenesulfonic acids, two further reactions appear. One of these is kinetically second order, involving the oxide and the anion of the acid; thus with hydrochloric acid

$$H_2C\underset{O}{\overbrace{\hspace{1.2cm}}}CH_2 + [\cdot\bar{C}l\cdot]^- \rightarrow [\cdot\bar{C}l - CH_2 - CH_2 - \bar{O}\cdot]^- \qquad (XXV)$$
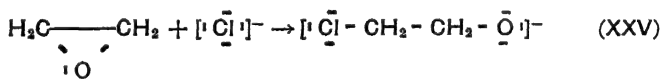
$$v_3 = k_3[S][Cl^-] \qquad (5)$$

The other leads to the same product but is kinetically third order, *e.g.*, with HCl

$$v_4 = k_4[S][Cl^-][OH_3^+] \qquad (6)$$

Some values of these constants for various ethylene oxide derivatives, all at 20° and at an ionic strength of 0.01, are listed in Table II.

Reaction (XXV) is unexpected, yet there can be no doubt of its existence. Without it the rate of reaction of the oxides with

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[14] WARD, *J. Chem. Soc.*, 445 (1927).

[15] BRØNSTED, KILPATRICK, and KILPATRICK, *J. Am. Chem. Soc.*, **51**, 428 (1929).

TABLE II.—SPECIFIC RATES OF ETHYLENE OXIDE REACTIONS[15]

Specific rate	Ethylene oxide	Glycide	Epichlor-hydrine	Cyclohexene oxide
k_1................	3.6×10^{-7}	2.8×10^{-7}	9.7×10^{-7}	
k_2................	5.33×10^{-3}	2.5×10^{-3}	4.1×10^{-4}	1.92
k_3 Cl⁻..........	....	5.7×10^{-6}	2.6×10^{-5}	
k_3 Br⁻..........	....	3.9×10^{-6}	1.4×10^{-4}	
k_3 SCN⁻........	....	3.0×10^{-4}	1.5×10^{-3}	
k_3 I⁻.............	....	6.2×10^{-4}	2.3×10^{-3}	
k_3 HCO₂⁻........	....	....	1.1×10^{-5}	
k_3 C₆H₅CO₂⁻.....	....	....	1.2×10^{-5}	
k_3 CH₃CO₂⁻......	....	....	1.4×10^{-5}	
k_3 (CH₃)₃CCO₂⁻ ..	....	....	1.9×10^{-5}	
k_4 HBr..........	0.20	0.13	0.05	
k_4 HCl..........	0.05	....	0.010	

0.1M KCl should be about one-millionth of the rate of reaction with 0.1M HCl, this being the ratio of the oxonium-ion concentrations; actually, the rate is about one-fiftieth as fast. Furthermore, the total rate of reaction in neutral, weakly acid, and weakly alkaline solutions is independent of the acidity, because reaction (XXV) is the predominant one under these conditions. Because of this reaction a solution of oxide in aqueous KCl becomes alkaline by virtue of the reaction

$$[\text{ClCH}_2\text{-}\text{CH}_2\text{-}\bar{\text{O}}\,]^- + \text{H}_2\text{O} \rightleftharpoons \text{ClCH}_2\text{CH}_2\text{OH} + \text{OH}^- \quad \text{(XXVI)}$$
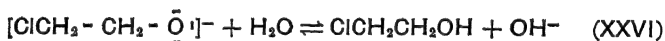
in a very few minutes. Most surprising of all, the reaction is easily detected with the wide variety of anions listed; yet a corresponding reaction with hydroxyl ion is not observed even in strongly alkaline solution.

The mechanism of reaction (XXV) is obviously a nucleophilic displacement on carbon, the displacing group being the halide ion, and the displaced one the bridge oxygen, but this remains attached to the molecule by virtue of the carbon-oxygen bond which is not involved in the displacement. That the reaction should go faster when the substituting group is chloride, acetate, or nitrate ion than when it is hydroxyl ion is a most striking example of the failure of the affinity of a reaction to measure its rate (page 137). The free-energy decrease accompanying the

reaction with hydroxyl ion must be much greater than that of the reaction with chloride ion, the mere fact that the chlorhydrine hydrolyzes quantitatively to the glycol demonstrates that; yet the reaction with chloride ion is the faster one. The comparative reluctance that hydroxyl ion here exhibits toward becoming attached to carbon appears in other reactions, most notably in the Schotten-Baumann acetylation procedure.

The acceleration of reactions (XXIV) and (XXV) by acids is normal. The addition of a proton to the ether oxygen in a reversible first step

$$H_2C{-}{-}{-}CH_2 + OH_3{}^+ \rightleftharpoons \left[H_2C{-}{-}{-}CH_2 \atop O \atop H \right]^+ + H_2O \quad (XXVII)$$
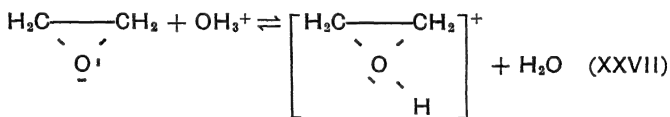
produces an intermediate in which the carbon-oxygen linkage is greatly weakened.

When the displacing group of reaction (XXV) is a carbanion such as the conjugate base of malonic ester, a new carbon-carbon linkage results, and the reaction becomes an effective method for preparing γ-hydroxyacids.

Since the displacement reaction (XXIV) must invert the configuration of the carbon atom on which it occurs, the two epoxybutanes

$$\begin{array}{cc} H_3C{-}C{-}H & H_3C{-}C \\ | \quad O & | \quad O \\ H_3C{-}C{-}H & H{-}C \\ & CH_3 \\ cis & trans \end{array}$$
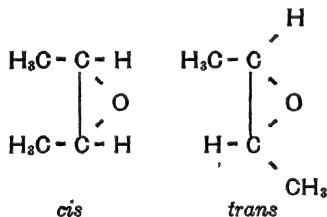
should give rise exclusively to the racemic and the meso glycol, respectively. The configurations are known beyond doubt from the existence of optically active forms of *trans* oxide and racemic glycol, and the prediction of an inversion of configuration has been confirmed experimentally.[16]

The Acetal and Ortho Ester Reactions.—Both the formation and the hydrolysis of the acetals, which are polyfunctional ethers,

[16] WILSON and LUCAS, *J. Am. Chem. Soc.*, **58**, 2396 (1936).

are catalyzed by acids. The hydrolysis in aqueous solution of the methyl, ethyl, and ethylene glycol acetals of acetaldehyde have been found to exhibit specific oxonium-ion catalysis,[17] and the same type of catalysis is observed in the reaction of acetaldehyde in ethanol.[18] It is probable that the reactions have a hemiacetal as an intermediate, the difficulty or impossibility of isolating this indicating that in the system

$$
R\text{-}CH\begin{matrix} O\text{-}R \\ \\ O\text{-}R \end{matrix} + H_2O \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} R\text{-}CH\begin{matrix} O\text{-}R \\ \\ O\text{-}H \end{matrix} + ROH \qquad (XXVIII)
$$

$$
R\text{-}CH\begin{matrix} O\text{-}R \\ \\ O\text{-}H \end{matrix} \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} R\text{-}CH = O + ROH \qquad (XXIX)
$$
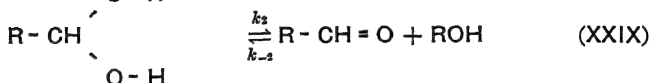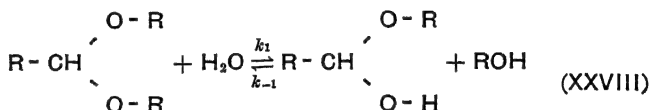
$k_2 \gg k_1$ and $k_{-2} \gg k_{-1}$ *i.e.*, the rate-determining step in both formation and hydrolysis is reaction (XXVIII). There is no reason to suppose that the mechanism of reaction (XXVIII) differs from that of other acid-catalyzed etherification and ether-hydrolysis reactions (page 300). Reaction (XXIX) offers an entirely different problem, which cannot be attacked experimentally in the present case but is probably closely related to that of the glucose mutarotation (page 337).

The relative hydrolysis rates of formaldehyde acetals of the following alcohols in water at 25° are[19]: methanol, 1; ethanol, 8.5; *i*-propanol, 47.2; *n*-propanol, 9.4; *i*-butyl alcohol, 13.0; *n*-butyl alcohol, 9.3. The structural effect suggests strongly that the reactions are of the solvolytic type with the process

$$
\begin{bmatrix} R & & \bar{O}\text{-}R \\ & \ddots C \ddots & \\ H & & \bar{O}\text{-}R \\ & & | \\ & & H \end{bmatrix}^+ \rightarrow \begin{matrix} R & & \bar{O}\text{-}R \\ & C & \\ H & & \bar{O}\text{-}H \end{matrix} + R^+ \qquad (XXX)
$$
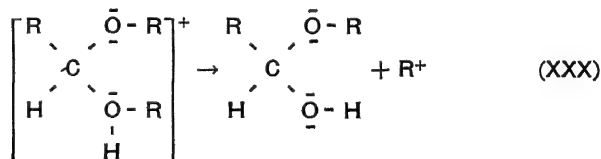
as the key step.

[17] BRØNSTED and WYNNE-JONES, *Trans. Faraday Soc.*, **25**, 59 (1929). BRØNSTED and GROVE, *J. Am. Chem. Soc.*, **52**, 1394 (1930).

[18] DEYRUP, *J. Am. Chem. Soc.*, **56**, 60 (1934).

[19] SKRABAL and EGER, *Z. physik. Chem.*, **122**, 349 (1926).

The relative hydrolysis rates of the acetals of pentaerythritol with various aldehydes are as follows[20]: HCHO, 1; CH$_3$CHO, 6000; CH$_3$CH$_2$CHO, 10,000; (CH$_3$)$_2$CHCHO, 4000; acetone, 10^7. Much information on hydrolysis rates of mixed acylalykl acetals of the type RCOOCH$_2$OR is also available.[21]

The hydrolysis of sucrose involves the rupture of an ether linkage of the acetal type, but the internal hemiacetals which are the result of a reaction analogous to (XXVIII) are the stable forms of the monosaccharides.

The hydrolysis of an ortho ester (page 218)

$$R - C\overset{\displaystyle OR}{\underset{\displaystyle OR}{-}}OR + H_2O \rightarrow R - C\overset{\displaystyle O-R}{\underset{\displaystyle O}{}} + 2ROH \qquad (XXXI)$$
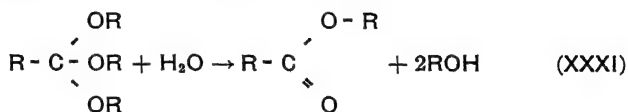
is a reaction of much the same sort as that of an acetal. The irreversibility which is one of its characteristics may be attributed to the greater saturation of the ester carbonyl compared with that of an aldehyde. Intermediates of the hemiacetal type are not isolable, and the mechanism is no doubt identical with that of the acetal hydrolysis. The acid catalysis may be of either the general acid or the specific oxonium-ion type (page 220).

The Conversion of Carbonium Ions to Heterocycles.—A carbonium ion may react internally to form a ring system. The conversion of a halogen amine to a cyclic ammonium ion

$$H_2\bar{N} - CH_2(CH_2)_xCH_2 - \bar{C}l \rightarrow [H_2\overline{N - CH_2(CH_2)_x}CH_2]^+ + [\cdot \bar{C}l \cdot]^- \quad (XXXII)$$
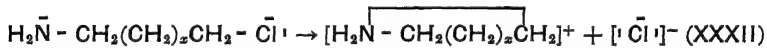
is first order, and its rate is independent of the concentration of hydroxyl ion.[22] It may involve an internal nucleophilic displacement or a process of the solvolytic type. The rate is greatest when the ring formed is one of five members; it does not change greatly for rings of more than 12 members. The polymerization, which is a wasteful side reaction in the preparative sense, especially with large rings, may be largely suppressed by working at low concentrations. This is because the polymeri-

[20] Skrabal and Zlatewa, *Z. physik. Chem.*, **119**, 305 (1926).

[21] Palomaa, Salmi, Janssen, and Sabo, *Ber.*, **68B**, 303 (1935).

[22] Salomon, *Trans. Faraday Soc.*, **32**, 153 (1936).

zation rate depends upon the square of the concentration of the reactant, the ring formation upon the first power.

Conversion of Carbonium Ions to Olefins.—A carbonium ion may react with a base to form an olefin

$$\left[\begin{array}{c} R \quad\quad R \\ | \quad\quad\nearrow \\ R - C - C \\ | \quad\quad\searrow \\ H \quad\quad R \end{array}\right]^{+} + B \rightleftharpoons R - \overset{R}{\underset{|}{C}} = \overset{R}{\underset{|}{C}} - R + BH^{+} \qquad (XXXIII)$$
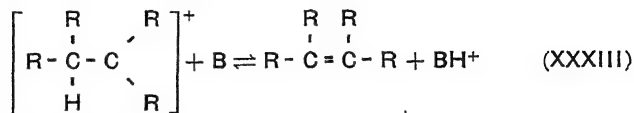
a process which merely reverses that by which olefins are converted to carbonium ions (page 292). Consequently, olefins may be produced by the solvolytic reaction of an alkyl halide in a suitable solvent, by the reaction of alkyl halide with silver ion, by the reaction of an alcohol with sulfuric acid, by a first-order decomposition reaction of a quaternary ammonium ion, by the action of nitrous acid on amines, in fact, by any of the procedures that lead to the formation of carbonium ions.

Evidence that formation of alcohol and of olefin from an alkyl halide pass through a common intermediate, the carbonium ion, has been obtained from the study of the relative amounts of the two substances formed from different sources of carbonium ion.[23] Thus the rate of the first-order reaction of *s*-octyl bromide in 60 per cent ethanol at 100° is 33 times greater than that of *s*-octyl chloride. Yet the ratio of octylene to octyl alcohol is 0.19 when the bromide reacts, 0.21 when the chloride reacts. With *t*-butyl halides at 25° in 80 per cent ethanol the first-order rates of reaction of chloride, bromide, and iodide are as 1:44:106; the ratios of olefin to alcohol produced are 0.202, 0.144, and 0.148. With *t*-amyl halides under the same conditions the olefin-alcohol ratios are 0.50, 0.26, and 0.25. The total rate of reaction is the rate of formation of the carbonium ion and varies greatly according to the halide used, whereas the composition of the product depends upon the behavior of the carbonium ion after it is formed. That the latter varies slightly with the nature of the halide adds further evidence that the reaction of the carbonium ion in a solvolytic reaction occurs before it has completely escaped from the influence of the halide ion.

[23] (a) HUGHES, INGOLD, and SCOTT, *J. Chem. Soc.*, 1271 (1937). (b) HUGHES, INGOLD, and SHAPIRO, *ibid.*, 1277. (c) COOPER, HUGHES, and INGOLD, *ibid.*, 1280. (d) HUGHES and MACNULTY, *ibid.*, 1283.

Olefins may also be formed from alkyl halides or from quaternary ammonium ions by a second-order reaction with a base, the mechanism of which obviously involves an attack by the base on a β-hydrogen atom[24]

$$R_2CH - CR_2Cl + OH^- \rightarrow [R_2C - CR_2Cl]^- + H_2O \qquad \text{(XXXIV)}$$
$$[R_2C - CR_2Cl]^- \rightarrow R_2C = CR_2 + Cl^- \qquad \text{(XXXV)}$$
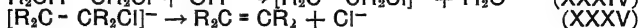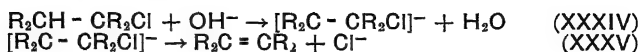
The reaction competes with the first-order olefin formation by way of the carbonium ion and with the two reactions that lead to alcohol. In the case of s-octyl bromide in a water-ethanol medium at 60° the specific rates of the four reactions are as follows:[23b] first-order alcohol formation, 4.66×10^{-5}; first-order olefin formation, 5×10^{-6}; second-order alcohol formation, 3.58×10^{-4}; second-order olefin formation, 4.39×10^{-4}. It follows from these figures that, in acid solutions in which both second-order reactions are suppressed by the low hydroxyl-ion concentration, there is 10 per cent olefin in the product; in alkaline solutions it may reach 55 per cent. The acid medium is, therefore, a much more favorable one for the preparation of the alcohol. Another stratagem that has been used to reduce the olefin by-product in the conversion of alkyl halide to alcohol is to react the halide with acetate ion and then to hydrolyze the acetate to the alcohol. The possibility of doing this is further evidence of the relatively low tendency of hydroxyl ion to attach itself to carbon. If the relative rates of attack of acetate ion and of hydroxyl ion were the same when they act upon protons as when they act upon alkyl groups, the two reactions would be equally affected by the use of one instead of the other base, and the proportion of olefin formed would be unchanged.

Acid-catalyzed Olefin Polymerization.—A carbonium ion may attach itself to an olefin carbon atom; if the carbonium ion is the conjugate acid of the olefin, the result is a polymerization of the olefin.[1]

$$\begin{array}{c} R \\ \diagdown \\ C = C \\ \diagup \quad \diagdown \\ H \qquad H \end{array} + HA \rightleftharpoons \left[\begin{array}{c} R \qquad R \\ | \\ H - C - C \\ | \qquad \diagdown \\ H \qquad H \end{array} \right]^+ + A^- \qquad \text{(XXXVI)}$$
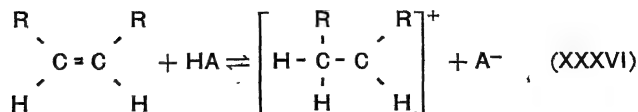
[24] HANHART and INGOLD, *J. Chem. Soc.*, 997 (1927). HUGHES, INGOLD, and PATEL, *ibid.*, 526 (1933).

$$
\begin{bmatrix} \overset{R}{\underset{H}{H-C-C}} \overset{R}{\diagdown} \end{bmatrix}^{+} + \overset{R}{\underset{H}{\diagup}} C = C \overset{R}{\underset{H}{\diagdown}} \rightarrow \begin{bmatrix} \overset{R}{\underset{H}{H-C-}}\overset{R}{\underset{H}{C-}}\overset{R}{\underset{H}{C-}} C \overset{R}{\diagdown} \end{bmatrix}^{+} \tag{XXXVII}
$$
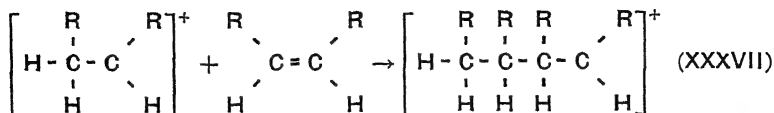
The product is still a carbonium ion, and it may react in various ways. If it loses a proton from the δ-carbon atom, a cyclobutane derivative (H) is formed; if the proton is lost from the β-carbon, the result is an olefinic dimer (I); if it reacts with a third olefin molecule to form (J), the system is well on its way toward a long-chain polymerization.

$$
\underset{(H)}{\overset{R\ H}{\underset{H\ R}{\underset{R-C-C-H}{H-C-C-R}}}} \qquad \underset{(I)}{\overset{R\ R\ R\ R}{\underset{H\ H\ \ \ H}{H-C-C-C=C}}} \qquad \underset{(J)}{\begin{bmatrix} \overset{R\ R\ R\ R\ R}{\underset{H\ H\ H\ H\ H}{H-C-C-C-C-C-C}} \overset{R}{\diagdown} \end{bmatrix}^{+}}
$$
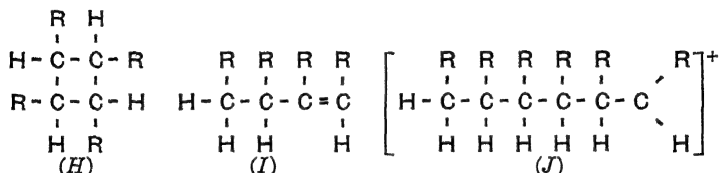
A kinetic study[25] of the similar polymerization of indole in 50 per cent ethanol has shown that the rates in $0.2M$ $HClO_4$ and $0.2M$ HCl are identical with each other and nearly the same as that produced by H_2SO_4 of the same electrometric pH. The reaction is, therefore, initiated by a proton transfer from oxonium ion, as in the olefin hydration (page 292). The dimerization of skatole in glacial acetic acid[25] is second order in skatole and also second order in the sulfuric acid catalyst. The latter effect is reminiscent of that observed in the ketone iodination in the same medium (page 274) and cannot be taken to indicate that two molecules of acid are involved. The mechanism of equations (XXXVI) and (XXXVII) leads to the following equations (S = olefin):

$$
v = \Sigma k_i[S][HA_i] \tag{7}
$$

$$
v = k[S]^2[OH_3^+] \tag{8}
$$

$$
v = \Sigma k_i[S]^2[HA_i] \tag{9}
$$

according as reaction (XXXVI) or (XXXVII) or the final loss of a proton is rate determining.

Since an alcohol may be converted to an olefin by way of a carbonium ion, the necessary conditions for the formation of olefin polymers are present in the reaction of alcohols with

[25] Schmitz-Dumont, Hamann, and Diebold, *Ber.*, **71B**, 205 (1938).

strong acids. The same consideration applies to the reaction of alkyl halides with silver salt and to the reaction of an amine with nitrous acid.

When the carbonium ion of reaction (XXXVII) is not the conjugate acid of the olefin, the reaction can no longer be called an olefin polymerization, even though its essential character is unchanged. The factors that affect the two functions of the olefin in reactions (XXXVI) and (XXXVII) are not necessarily the same. Thus dianisylethylene does not polymerize alone but does condense with skatole under the influence of strong acids.[25]

Reaction of Carbonium Ions with Aromatic Compounds: Friedel-Crafts Reaction.—The net effect of reaction (XXXVII) followed by the loss of a proton to form (*I*) is a displacement by a carbonium ion of a proton attached to unsaturated carbon. If the latter is aromatic, the reaction system becomes immediately a model for the Friedel-Crafts reaction and its close relatives. In such cases it seems probable that the displacement occurs in one step, because this avoids the necessity of overcoming the resonance energy of the aromatic substance

$$R_3C^+ + C_6H_6 + B \rightarrow R_3CC_6H_5 + BH^+ \qquad (XXXVIII)$$

The chemical inertia of these reactions and the nature of the condensing agents necessary vary with both the ease of formation of the carbonium ion and the reactivity of the aromatic hydrocarbon. This suggests that the condensation reaction rather than the formation of the ion is rate determining. *t*-Butyl and triphenylmethyl bromides react spontaneously and rapidly with excess of phenol at 90°, benzyl bromide less rapidly, and *i*-propyl bromide still more slowly.[26] In every case the alkyl group becomes attached to nuclear carbon, not to oxygen. Michler's hydrol $[(CH_3)_2NC_6H_4]_2CHOH$ condenses with the more reactive aromatics (*e.g.*, dimethylaniline) in dilute aqueous hydrochloric acid.[27] The already large tendency toward formation of the carbonium ion possessed by benzhydrol is greatly enhanced by the electron-repelling amine groups. Secondary and tertiary aliphatic alcohols condense with benzene or naphthalene in

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[26] BENNETT and REYNOLDS, *J. Chem. Soc.*, 131 (1935).

[27] DRP 27032 (1883). Frdl. I, 75.

70 to 80 per cent sulfuric acid.[28] Liquid hydrogen fluoride,[29] boron fluoride,[30] and aluminum chloride[31] are also effective with alcohols. With reagents as powerfully electrophilic as these, it makes little difference whether the alkyl derivative is a halide as in the classical Friedel-Crafts procedure or an alcohol, an ether, an ester, or even an olefin. All these may be converted to a carbonium ion by an electrophilic reagent, and all of them enter into reactions of the Friedel-Crafts type with any of the condensing agents noted above.

Aluminum chloride gives conducting solutions in C_2H_5Cl as does aluminum bromide in C_2H_5Br,[32a] and transference experiments indicate that the aluminum is in the anion. The mobile equilibrium

$$C_2H_5Cl + AlCl_3 \rightleftharpoons C_2H_5^+ + AlCl_4^- \qquad \text{(XXXIX)}$$
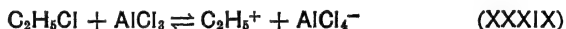
which these facts suggest is consistent with the carbonium-ion mechanism for the Friedel-Crafts reaction, as is also the fact that the HCl produced in the reaction is in radioactive equilibrium with the aluminum chloride, when active aluminum chloride is used.[32b]

Methyl and ethyl groups may be introduced only by the most active condensing agents aluminum chloride and boron fluoride. Normal alkyl halides with longer carbon chains than the ethyl derivatives yield rearranged secondary and tertiary alkyl benzenes, a behavior typical of reactions with carbonium-ion intermediates. Cyclodehydrations[33] are internal condensations of the Friedel-Crafts type which are induced by moderately strong sulfuric acid when an aromatic compound carries a hydroxyl

[28] MEYER and BERNHAUER, *Monatsh.*, **53/54**, 721 (1929).

[29] SIMONS and ARCHER, *J. Am. Chem. Soc.*, **60**, 986; 2952 (1938). SIMONS, ARCHER, and PASSINO, *ibid.*, **60**, 2956 (1938).

[30] MEERWEIN, *Ber.*, **66B**, 411 (1933). SLANINA, SOWA, and NIEUWLAND, *J. Am. Chem. Soc.*, **57**, 1547 (1935). PRICE and CISKOWSKI, *ibid.*, **60**, 2499 (1938).

[31] BOWDEN, *J. Am. Chem. Soc.*, **60**, 645 (1938).

[32] (a) WERTYPOROCH et al., *Z. physik. Chem.*, **A162**, 398 (1932); **A168**, 31; 124 (1934). WOHL and WERTYPOROCH, *Ber.*, **64B**, 1357 (1931). (b) FAIRBROTHER, *J. Chem. Soc.*, 503 (1937).

[33] BOGERT and DAVIDSON, *J. Am. Chem. Soc.*, **56**, 185 (1934). PRICE, DAVIDSON, and BOGERT, *J. Org. Chem.*, **2**, 540 (1938).

grcup or a halogen atom on the γ- or δ-carbon of a side chain containing five to seven carbon atoms or when one of these carbons is unsaturated. A ring of five or six members is formed, directly in the preceding case, indirectly by a rearrangement when the hydroxyl halogen or unsaturation is on another carbon atom.

The product obtained from the action of sulfuric acid on a mixture of olefin and aromatic compound varies in an interesting and predictable fashion with the concentration of the acid.[34] In 70 per cent acid the product from *i*-butene is predominantly alkyl sulfuric acid, formed by the action of the conjugate acid of the olefin on bisulfate ion

$$[(CH_3)_2C \cdot CH_3]^+ + HSO_4^- \rightarrow (CH_3)_3COSO_3H \qquad (XL)$$
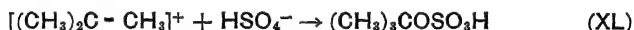
With increase in acid concentration the concentration of bisulfate ion decreases, and in 80 per cent acid the chief reaction is a polymerization of the olefin, which requires the simultaneous presence of the olefin and its conjugate acid (page 308). With still further increase in acid concentration the conversion of the olefin to the conjugate acid becomes more complete, the rate of the polymerization decreases because of the decreasing concentration of olefin, and in 96 per cent sulfuric acid the product is almost exclusively butylbenzene. A similar sequence must determine the choice of condensing agent and alkyl or acyl derivative for optimum yield in any reaction of the Friedel-Crafts type.

The alkylation of benzene with paraffins under the action of aluminum chloride plus hydrogen chloride[35] must depend upon the great acid strength of $HAlCl_4$ and take the course

$$R_3'C \cdot CR_3'' + HAlCl_4 \rightarrow R_3'CH + [CR_3'']^+ + AlCl_4^- \qquad (XLI)$$
$$[CR_3'']^+ + C_6H_6 \rightarrow R_3''CC_6H_5 + H^+ \qquad (XLII)$$
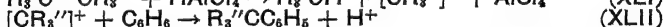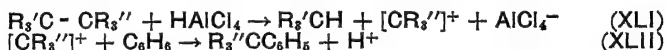
The relative ease with which the reaction occurs when the group CR_3'' is *t*-butyl is consistent with the low activation energy usually associated with the formation of the *t*-butyl ion. Thus the hydrocarbon $CH_3—CH_3—CH(CH_3)—C(CH_3)_3$ reacts readily at 80° and measurably at 0°, yielding *t*-butylbenzene and *n*-butane.

[34] IPATIEFF, CORSON, and PINES, *J. Am. Chem. Soc.*, **58**, 919 (1936).
[35] GROSSE, MAVITY, and IPATIEFF, *J. Org. Chem.*, **3**, 137 (1938).

Other Substitution Reactions of Aromatic Compounds: Halogenation: Nitration.—The typical substitution reactions of aromatic compounds are favored by strong acids and other electrophilic reagents and give every evidence of being electrophilic displacements on aromatic carbon of the same type as the Friedel-Crafts reaction. Nuclear halogenation is strongly aided by aluminum or ferric halides, which must favor the process

$$\text{\textperiodcentered}\,\bar{Br} - \bar{Br}\,\text{\textperiodcentered} + AlBr_3 \rightleftharpoons [\text{\textperiodcentered}\,\bar{Br}]^+ + AlBr_4{}^- \tag{XLIII}$$
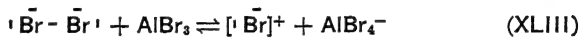
just as they do the carbonium-ion formation from alkyl halides,[36] and the positive halogen ion must displace a proton from the aromatic substance just as a carbonium ion does

$$Br^+ + C_6H_6 \rightarrow BrC_6H_5 + H^+ \tag{XLIV}$$
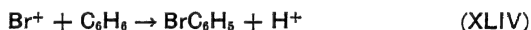
Iodination of benzene may be induced by the action under anhydrous conditions of silver perchlorate and iodine,[37] presumably by way of the reaction

$$\text{\textperiodcentered}\,\bar{I} - \bar{I}\,\text{\textperiodcentered} + Ag^+ \rightarrow \text{\textperiodcentered}\,\bar{I} - Ag + [\text{\textperiodcentered}\,\bar{I}]^+ \tag{XLV}$$
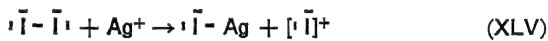
or by the action of the brown solutions that are obtained by the reaction of iodine pentoxide with excess of iodine in concentrated sulfuric acid.[38] These appear to contain ions of the type $I_3{}^+$ and $I_5{}^+$ which are active iodinating agents. Sulfuric acid solutions that contain iodine pentoxide and iodine in the proportions that correspond to I_2O_3 readily form iodoso derivatives by reaction with benzene, probably by way of an IO^+ ion.[39] The catalytic effect of iodine on nuclear bromination may be attributed to the action of BrI, which should be a more active brominating agent than BrBr in the same way that CH_3I is a more effective methylating agent than CH_3Br.

The side-chain halogenation of toluene and the *addition* of halogen to aromatic hydrocarbons are reactions of the radical type (page 376).

[36] BRUNER *et al.*, *C. A.*, **2**, 1272 (1908); **4**, 3067 (1910); **5**, 3045 (1911). KHARASCH, WHITE, and MAYO, *J. Org. Chem.*, **3**, 33 (1938). PRICE and ARNTZEN, *J. Am. Chem. Soc.*, **60**, 2835 (1938).

[37] BIRKENBACH and GOUBEAU, *Ber.*, **65B**, 395; 1339 (1932); **66B**, 1280 (1933); **67B**, 917 (1934).

[38] MASSON, *J. Chem. Soc.*, 1708 (1938).

[39] MASSON and HANBY, *J. Chem. Soc.*, 1699 (1938).

Like halogenation, nitration may apparently be either of the radical type or of the nature of an electrophilic displacement on carbon. Nitrations with nitric acid alone or in nonpolar solvents, especially when fuming acid is used, have all the earmarks of the former class of reactions; nitration by the usual sulfuric acid-nitric acid mixture has the characteristics of the latter. Nitration with mixed acid proceeds at a technically useful rate only when the ratio of the number of moles of H_2SO_4 to the sum of the numbers of moles of H_2O and HNO_3 exceeds a certain ratio, which happens to be unity in the case of benzene.[40] Since nitric acid and water are bases with respect to sulfuric acid, this means that the reaction rate is a function of the acidity of the solution.

The actual nitrating agent is not known. A nitrogen atom with only six valence electrons is present in the important resonating structures (K) and (L) of the ions, which nitric acid is known to form at high acidities (page 47), as well as in the structure (M) involved in another possible ion.

$$\left[\underset{(K)}{\overset{\overset{\displaystyle \ddot{O}-H}{\diagup}}{\cdot \ddot{O}-N \underset{\diagdown}{} \ddot{O}-H}} \right]^{+} \qquad \left[\underset{(L)}{\overset{\overset{\displaystyle \ddot{O}-H}{\diagup}}{H-\ddot{O}-N \underset{\diagdown}{} \ddot{O}-H}} \right]^{++} \qquad [\cdot \underset{(M)}{O = N - \ddot{O} \cdot}]^{+}$$
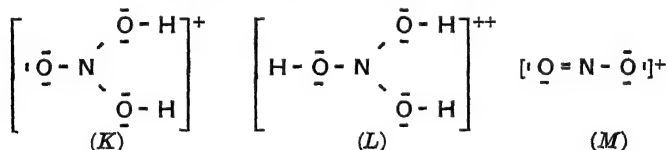
The kinetics can be studied only with relatively unreactive benzene derivatives which, in addition, are moderately soluble in strong sulfuric acid. Data are available for nitrobenzene, benzoic acid, benzenesulfonic acid, and anthraquinone; in each case the rate goes through a maximum with increasing acid concentration.[41] With nitrobenzene the rate is three times faster in 95 per cent sulfuric acid than in 100 per cent; with benzoic acid the same ratio is more than 28. Since the status of dissolved benzoic acid is constant over this range of acidity [as $C_6H_5-C(OH)_2^+$], the decrease in rate must be due to the protolytic conversion of nitric acid from a more reactive to a less reactive form, a conclusion that is supported by the fact that all sub-

[40] GROGGINS, "Aniline and Its Derivatives," New York, 1924, p. 72. HETHERINGTON and MASSON, *J. Chem. Soc.*, 105 (1933).

[41] MARTINSEN, *Z. physik. Chem.*, **50**, 385 (1905); **59**, 605 (1907). LAUER and ODA, *J. prakt. Chem.*, **144**, 176; **146**, 61 (1936).

strates show a qualitatively similar effect. The decrease in nitrogen content of nitrocellulose produced at very high sulfuric acid concentrations[42] may very well have the same cause.

Sulfonation rates increase with increasing acid concentration in sulfuric acid of less than 100 per cent concentration and with the concentration of SO_3 in fuming acid.[43] A possible course is the electrophilic displacement

$$SO_3 + C_6H_6 \rightarrow C_6H_5SO_3^- + H^+ \qquad (XLVI)$$
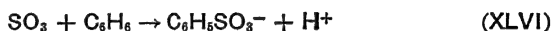
The coupling of a diazonium salt with aniline or phenol may be attributed to the displacement

$$[C_6H_5 - \bar{N} = \bar{N}]^+ + C_6H_5N(CH_3)_2 \rightarrow C_6H_5 - \bar{N} = \bar{N} - C_6H_4N(CH_3)_2 + H^+ \qquad (XLVII)$$
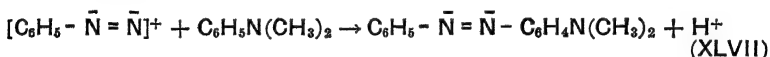
The well-known fact that the high acidity necessary for the diazotization of an amine must be decreased by the addition of carbonate, bicarbonate, or acetate ion before the coupling is obviously due to the fact that aniline and phenolate ion are more reactive in nuclear substitution reactions than are anilinium ion and phenol.

The rate of coupling of various diazonium salts with a variety of phenols has been found[44] to be proportional to the hydroxyl-ion concentration. A general base catalysis can be definitely excluded for acetate ion and probably for other bases except hydroxyl ion. Electron-attracting groups like p-nitro in the diazonium ion favor the coupling, which is to be expected, since a low electron density on the coupling nitrogen should give it a greater affinity for the electrons of the phenolate ion. The relative rates for various substituents in the diazonium ion are p-NO_2, 1300; p-SO_3^-, 13; p-Br, 13; none, 1; p-CH_3, 0.4; p-CH_3O, 0.1. To within 25 per cent the rate is the same for five different phenols, mostly naphthol sulfonic acids.

Presumably the favorable effect of increasing hydroxyl-ion concentration reaches an upper limit when the conversion of the diazonium ion to the diazonium hydroxide (page 295) becomes significant.

[42] Farmer, J. Soc. Chem. Ind., **50**, 75T (1931).
[43] Martinsen, Z. physik. Chem., **62**, 713 (1908). Pinnow, Z. Elektrochem., **21**, 380 (1915); **23**, 243 (1917).
[44] Conant and Peterson, J. Am. Chem. Soc., **52**, 1220 (1930).

Racemization.—A partial but usually incomplete racemization is one of the most characteristic features of reactions in which a more or less free carbonium ion is an intermediate. This is observed not only in the solvolytic reaction of alkyl halides but also in the action of HCl on alcohols and in that of nitrous acid on amines (page 180).

Rearrangements: Anionotropic Reactions.—Quite as characteristic of carbonium ions as racemization is rearrangement. The simplest case, since it involves only electron shifts, is the *anionotropic* rearrangement, which requires the presence of an olefin linkage adjacent to the carbonium carbon. Thus the carbonium ion produced by the action of acids on C_6H_5—CHOH—CH=CH_2 must contain the resonating structures (N).

$$[C_6H_5 \text{-} CH \text{-} CH = CH_2 \longleftrightarrow C_6H_5 \text{-} CH = CH \text{-} CH_2]^+$$
$$(N)$$
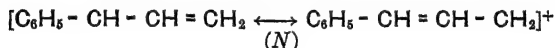
In the first the carbon alpha to the phenyl is positive, in the other the gamma carbon. The reaction of the ion with bromide ion may, therefore, form either C_6H_5—CHBr—CH=CH_2 or C_6H_5—CH=CH—CH_2Br without the shift of so much as a hydrogen atom.[45] To the extent that the latter product predominates, as it does in this case, the reaction involves a rearrangement of α-phenylallyl alcohol to a derivative of cinnamyl alcohol. As is to be expected if the reaction of both alcohols goes through the common intermediate (N), cinnamyl alcohol is converted by HBr to cinnamyl bromide without rearrangement. The product in this case is the thermodynamically more stable bromide, but this need not be so, since the composition of the reaction product depends upon the relative rates of reaction of (N) in the two possible directions, not upon the relative equilibrium constants of the two reactions (page 180).

The only reasonable interpretation of these rearrangements is the carbonium-ion one. The rearrangement is produced by reagents that are known to favor the formation of the carbonium ion, *e.g.*, by the action of acids on alcohols or by the solvolytic reaction of esters, especially those of strong acids, in media favorable to ionization. The rearrangement cannot be internal since α-phenylallyl p-nitrobenzoate, which rearranges to cinn-

[45] BURTON and INGOLD, *J. Chem. Soc.*, 904; 1650 (1928); 455 (1929).

amyl *p*-nitrobenzoate in acetic anhydride, yields large amounts of cinnamyl acetate when the anhydride contains tetramethyl ammonium acetate as a source of acetate ions.[45] The rearrangement is facilitated by the kind of structure of reactant that favors carbonium-ion formation; thus α-phenylallyl derivatives are more easily rearranged than α-methylallyl derivatives. When the reactant contains an asymmetric carbinol carbon, the reaction product is largely but not always completely racemized.[46]

A reaction that involves a rearrangement may be accompanied by a direct nucleophilic displacement, which apparently leads no more to rearrangement than it does to racemization. Thus the reaction of cinnamyl chloride with potassium acetate, *i.e.*, acetate ion, in acetic anhydride is kinetically of the second order and is, therefore, a nucleophilic displacement. The product is exclusively cinnamyl acetate. The reaction of the same chloride in acetic acid without the addition of acetate ion has an order between first and second, and the reaction product is a mixture of cinnamyl and α-phenylallyl acetates.[47]

Similarly, the reaction of crotyl alcohol or of its isomer methyl vinyl carbinol with HBr yields a mixture of the isomeric bromides, but a larger proportion of crotyl bromide is formed from crotyl alcohol than from the isomer.[48] The magnitude of the effect depends upon the conditions, the largest difference appearing when the reaction is carried out in glacial acetic acid at 0° when crotyl alcohol yielded 83.4 per cent crotyl bromide and methyl vinyl alcohol formed only 71.5 per cent of the same substance.

The unsaturated carbonium ions, which are the characteristic intermediates in the anionotropic rearrangement, may also be formed by the addition of a proton to a conjugated diene

$$R - CH = CH - CH = CHR + HA \rightleftharpoons [R - CH \overline{} CH \overline{} CH - CH_2R]^+ + A^-$$
$$\text{(XLVIII)}$$
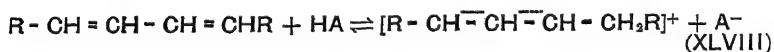
If hydroxyl or chloride ion then adds to the carbonium ion, the total reaction represents a 1:2 or a 1:4 addition to the original unsaturated system according to the way in which it adds

[45] KENYON, PARTRIDGE, and PHILLIPS, *J. Chem. Soc.*, 207 (1937). ARCUS and KENYON, *ibid.*, 1912 (1938).

[47] MEISENHEIMER and BEUTTER, *Ann.*, **508**, 58 (1934).

[48] YOUNG and LANE, *J. Am. Chem. Soc.*, **60**, 847 (1938).

$$[R - CH \overline{} CH \overline{} CH - CH_2R]^+ + OH^- \Big\langle \begin{array}{l} R - CH = CH - CHOH - CH_2R \\ 1:2 \quad (XLIX) \\ R - CHOH - CH = CH - CH_2R \\ 1:4 \quad (L) \end{array}$$
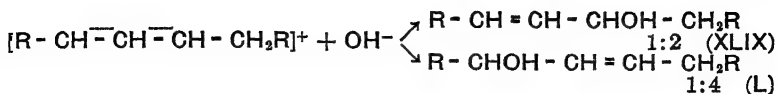
In view of the evidence that addition to the double bond is a two-step process (page 147), this is by all odds the most probable explanation of the 1:4 addition.

The acid-catalyzed *cis-trans* rearrangement of maleic to fumaric acid must involve a similar intermediate (O)

$$\left[\begin{array}{c} \overset{|\overset{\cdot}{\text{O}}}{\underset{\text{H}}{\text{H} - \overset{\cdot}{\text{O}} - \overset{||}{\text{C}} - \text{CH} = \text{CH} - \text{C}}} \overset{\overset{\cdot}{\text{O}} - \text{H}}{\underset{\overset{\cdot}{\text{O}} - \text{H}}{}} \longleftrightarrow \text{H} - \overset{\cdot}{\text{O}} - \overset{\overset{|\overset{\cdot}{\text{O}}}{||}}{\text{C}} - \text{CH} - \text{CH} = \text{C} \overset{\overset{\cdot}{\text{O}} - \text{H}}{\underset{\overset{\cdot}{\text{O}} - \text{H}}{}} \end{array} \right]^+$$

$$(O)$$
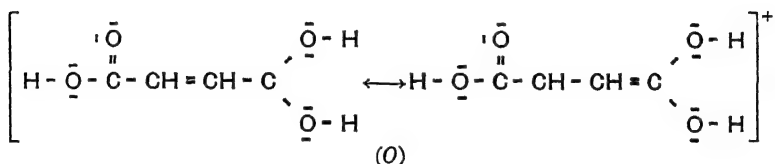
in which the middle bond acquires enough single-bond character to permit rotation to the fumaroid configuration. The intermediate cannot be [HOOC—CH$_2$—CH—COOH]$^+$, formed by addition of a proton to carbon, because the fumaric acid produced is free of deuterium when the reaction occurs in deuterium water.[49]

Rearrangements Involving a Change in the Carbon Skeleton.— All rearrangements involving a change in the carbon skeleton may be accounted for by a hypothesis of Whitmore[50] as follows: a carbonium ion is formed, and an alkyl group together with its bonding pair shifts from a neighboring carbon atom to the carbonium carbon. The direction of the shift is usually such that the new carbonium carbon carries a greater number of alkyl groups than the old one. These effects are especially well illustrated in the neopentyl derivatives, in which all reactions of the carbonium-ion type yield exclusively rearranged products. Thus the iodide $(CH_3)_3CCH_2I$ is converted by silver acetate to the rearranged acetate $(CH_3)_2C(OAc)CH_2CH_3$;[51] the alcohol $(CH_3)_3C$-CH_2OH is converted by HBr to the corresponding bromide $(CH_3)_2CBrCH_2CH_3$;[52] the amine $(CH_3)_3CCH_2NH_2$ is converted

[49] Horrex, *Trans. Faraday Soc.*, **33**, 570 (1937).
[50] Whitmore, *J. Am. Chem. Soc.*, **54**, 3274 (1932).
[51] Whitmore and Fleming, *J. Chem. Soc.*, 1269 (1934).
[52] Whitmore and Rothrock, *J. Am. Chem. Soc.*, **54**, 3431 (1932).

by nitrous acid to the alcohol $(CH_3)_2COHCH_2CH_3$;[53] and the alcohol $(CH_3)_3CCH_2OH$ is converted by sulfuric acid to the rearranged olefins $(CH_3)_2C=CHCH_3$ and $CH_2=C(CH_3)CH_2CH_3$. These reagents are all calculated to produce a carbonium ion, and the products are all accounted for if the ion rearranges

$$\left[\begin{array}{c} CH_3 \quad H \\ CH_3-C-C \\ CH_3 \quad H \end{array} \right]^+ \rightarrow \left[\begin{array}{c} H_3C \quad CH_3 \\ C-C-H \\ H_3C \quad H \end{array} \right]^+ \qquad (LI)$$
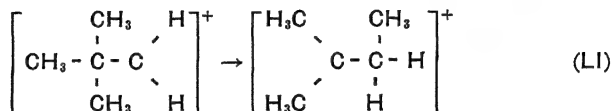
before reacting further.

Rearrangements of this type, which are called Wagner-Meerwein rearrangements, are frequent and important features of the reactions of terpenes. They have been studied in an especially detailed and useful way in the rearrangement of camphene hydrochloride to isobornyl chloride.

$$(LII)$$
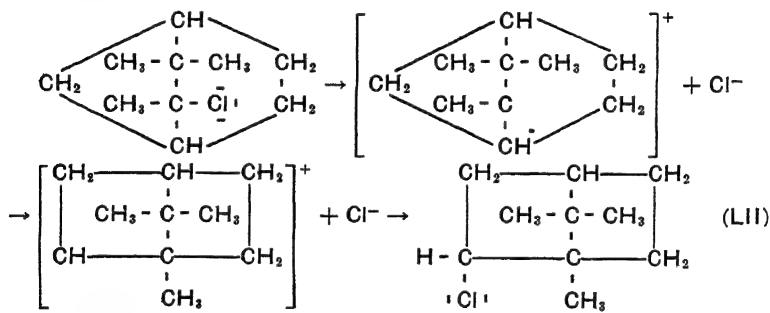
As equation (LII) shows, the change may be accounted for by the Whitmore hypothesis. The reaction shows all the characteristics of a carbonium-ion intermediate.[54] Thus it is practically instantaneous in cresol and in sulfur dioxide, the very solvents in which the ionization of triphenylmethyl chloride is most extensive (page 53), and in general the rate parallels the ionization. In chlorbenzene the half time of the reaction at 40° is 56 hr., yet it becomes practically complete in 5 min. at 20° in the presence of a 0.001N concentration of the electrophilic

[53] FREUND and LENZE, Ber., 24, 2150 (1891).

[54] (a) MEERWEIN and VAN EMSTER , Ber., 55, 2500 (1922).   (b) BARTLETT and PÖCKEL, J. Am. Chem. Soc., 60, 1585 (1938).

reagents $SbCl_5$ or $SnCl_4$. It is also strongly accelerated by $HgCl_2$, $FeCl_3$, and $SbCl_3$, in fact by all halides of the type that have an affinity for chloride ion and favor the ionization of triphenyl chloride. The reaction is faster with the bromide and with the chlorcymolsulfonate, slower with the trichloracetate than with the chloride, again paralleling the ionization tendency. In nitrobenzene the rate is increased by HCl, a phenomenon that also parallels the ionization of triphenylmethyl halides (page 54). That the effect of the HCl is of the nature of the one on the ionization rather than one due to the chloride ion is demonstrated[54b] by the fact that lithium chloride has little effect on the rate.

Camphene hydrochloride exists in mobile equilibrium with HCl and the cyclic olefin camphene; consequently, it furnishes the HCl catalyst for its own rearrangement if none is added. Under these conditions the rate law is

$$v = \frac{[\text{camphene HCl}]^2}{[\text{camphene}]} \tag{10}$$

The carbon atom to which the chlorine is attached in isobornyl chloride is asymmetric; consequently, two stereoisomers may be formed from the ionic intermediate in proportions that depend upon the relative rates of their formation. The product that is most rapidly formed, isobornyl chloride, is not so stable as its stereoisomer bornyl chloride and rearranges slowly into it.

In similar rearrangements in which the molecule contains only one center of asymmetry, the reaction product has always been found to retain at least some of its activity.[55] The rearrangements behave, therefore, in the same way as the solvolytic reactions and related processes, in which a carbonium ion is formed but reacts further before it has completely lost the recollection of its original configuration. To the extent that the reaction product is optically active, the configuration on the asymmetric carbon should be inverted unless special steric factors enter into play.

Hydride Shifts.—The group that shifts may be a hydrogen atom with its bonding pair, *i.e.*, a hydride ion. In this way the

[55] WALLIS and BOWMAN, *J. Org. Chem.*, **1**, 383 (1936).

carbonium ion derived from a normal propyl compound is converted to an isopropyl ion

$$
\left[\begin{array}{c} \text{H}\ \ \text{H}\ \ \ \ \ \text{H} \\ |\ \ \ \ |\ \ \ \ \ \ \nearrow \\ \text{H-C-C-C} \\ |\ \ \ \ |\ \ \ \ \ \searrow \\ \text{H}\ \ \text{H}\ \ \ \ \ \text{H} \end{array}\right]^{+} \rightarrow \left[\begin{array}{c} \text{H}\ \ \ \ \ \text{H} \\ |\ \ \ \ \ \ \ | \\ \text{H-C-C-C-H} \\ |\ \ \ \ |\ \ \ \ | \\ \text{H}\ \ \text{H}\ \ \text{H} \end{array}\right]^{+} \qquad \text{(LIII)}
$$
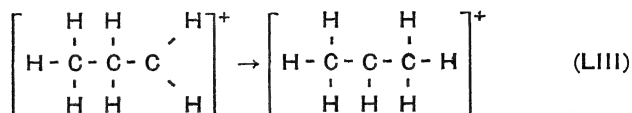
By means of this kind of shift the Friedel-Crafts reaction of *n*-propyl chloride yields *i*-propylbenzene, and the action of nitrous acid on *n*-propyl amine leads to *i*-propyl alcohol. The hydride shift is an entirely different process from the prototropic reaction (page 232); it is internal and spontaneous rather than external and dependent upon the intervention of an acid or base catalyst; it is the shift of a hydride ion instead of a proton, and the hydrogen moves one not two carbon atoms.

The Pinacol Rearrangement.—The pinacol rearrangement may be initiated by the action of acid on a glycol, its classical form, by the action of silver ion on a bromhydrine,[56] or by that of nitrous acid on an α-amino alcohol.[57] Obviously, therefore, it goes by way of a carbonium-ion intermediate. The reaction product can always be accounted for by the Whitmore hypothesis

$$
\left[\begin{array}{c} \text{R}'\ \ \text{R}'' \\ |\ \ \ \ | \\ \text{R}'-\text{C}-\text{C}-\text{R}'' \\ |\ \ \ \ \ \ \ | \\ \text{H-O} \end{array}\right]^{+} \rightarrow \left[\begin{array}{c} \text{R}' \\ | \\ \text{R}'-\text{C}\text{——}\text{C-R}'' \\ |\ \ \ \ \ \ \ | \\ \text{H-O}\ \ \ \ \text{R}'' \end{array}\right]^{+} \qquad \text{(LIV)}
$$
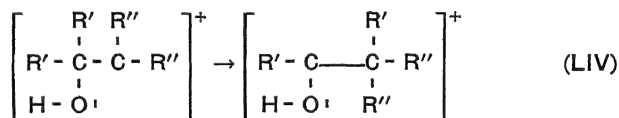
The product of reaction (LIV) is the conjugate acid of the ketone $\text{R}'\text{CO}$—$\text{CR}'\text{R}_2''$, which is the product isolated.

The migrating group attaches itself to the carbon to which it migrates on the side opposite that from which the hydroxyl, chlorine, or amine group was removed; hence, the configuration of this carbon is inverted.[58] This requirement may determine which of two possible groups migrates. In the relatively rigid structure of the 1,2-dimethylcyclohexane-1,2-diols the *cis* compound in 20 per cent sulfuric acid yields as sole product 2,2-di-

[56] AYERS, *J. Am. Chem. Soc.*, **60**, 2957 (1938).

[57] McKENZIE and RICHARDSON, *J. Chem. Soc.*, **123**, 79 (1923).

[58] BARTLETT and PÖCKEL, *J. Am. Chem. Soc.*, **59**, 820 (1937); BARTLETT and BAVLEY, *ibid.*, **60**, 2416 (1938).

methylcyclohexanone, and the *trans* compound forms 1-methyl-1-acetylcyclopentane.   In the first case the methyl group migrates because it is in position to fall in on the side of the carbonium carbon opposite to that from which the hydroxyl is being removed; in the second case a ring carbon is in a similarly favorable situation, and its migration converts the cyclohexane ring to a cyclopentane one.

In 1,2-dimethylcyclopentane-1,2-diol the *cis* compound rearranges easily to 2,2-dimethylcyclopentanone by migration of a methyl group.   But the migration of the ring carbon in the *trans* isomer would lead to a highly strained cyclobutane derivative; consequently, other reactions intervene and only tars can be isolated.

The stereochemical specificity observed in these rearrangements is closely analogous to the incomplete racemization found in solvolytic reactions and must have the same cause, the further reaction of the carbonium ion before it is completely free.

The Benzilic Acid Rearrangement.—This reaction

$$H_2O + C_6H_5 - CO - CO - C_6H_5 \rightarrow (C_6H_5)_2C(OH)COOH \qquad (LV)$$
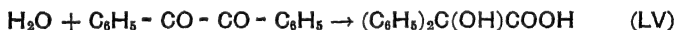
exhibits a specific hydroxyl-ion catalysis with no measurable catalysis by the bases phenolate ion and *o*-chlorphenolate ion.[59] Furthermore, the rate of rearrangement is slower than the likewise base-catalyzed oxygen exchange.[60]   It follows that the rate is proportional to the concentration of the ion (P) formed by the reversible addition of hydroxyl ion to one carbonyl group. The reaction can, therefore, be accounted for by the shift of a phenyl group with its bonding pair

$$\left[\begin{array}{c} C_6H_5 \\ | \\ H - \bar{O} - C \!\!-\!\!\!-\!\!\!-\!\! C - C_6H_5 \\ | \quad\;\; \| \\ {}^{\cdot}O^{\cdot} \;\; {}^{\cdot}\underset{-}{O} \end{array} \right]^{-} \rightarrow \left[\begin{array}{c} C_6H_5 \\ | \\ H - \bar{O} - C \!\!-\!\!\!-\!\!\!-\!\! \underset{|}{C} - C_6H_5 \\ \| \quad\;\; {}^{\cdot}\underset{-}{O}{}^{\cdot} \\ {}^{\cdot}\underset{-}{O} \end{array} \right]^{-} \qquad (LVI)$$

$$(P) \qquad\qquad\qquad\qquad (Q)$$
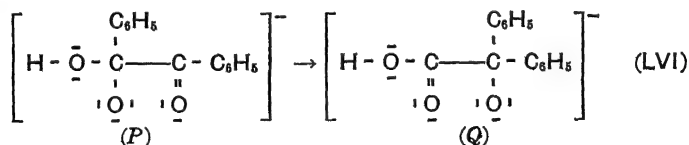
The addition of a proton to (Q) yields benzilic acid.   The reaction is, in essence, similar to the Wagner-Meerwein rearrangement, the carbon atom of the carbonyl group in (P) carries only

[59] WESTHEIMER, *J. Am. Chem. Soc.*, **58**, 2209 (1936).
[60] ROBERTS and UREY, *J. Am. Chem. Soc.*, **60**, 880 (1938).

six electrons in one of the resonating structures, and the rearrangement consists in the shift to this carbon from the adjacent carbon of a phenyl group along with its bonding pair. It differs in the sense that the carbonyl carbon is only weakly electrophilic and that the deficiency is made up by a high electron density in the neighborhood of the migrating group. The negative phenyl group is pushed by this rather than pulled by a high concentration of positive charge.

The Beckmann Rearrangement and Related Reactions.—The Beckmann rearrangement is a Wagner-Meerwein rearrangement in which the migrating group shifts from carbon to a positive nitrogen atom[61]

$$\begin{matrix} R' - C - R'' \\ \| \\ N - O - H \end{matrix} + H_2SO_4 \rightarrow \left[\begin{matrix} R' - C - R'' \\ \| \\ N \end{matrix} \right]^+ + H_2O + HSO_4^- \quad \text{(LVII)}$$

$$\left[\begin{matrix} R' - C - R'' \\ \| \\ N \end{matrix} \right]^+ \rightarrow \left[\begin{matrix} C - R'' \\ \| \\ R' - N \end{matrix} \right]^+ \quad \text{(LVIII)}$$

$$[R' - N \equiv C - R'']^+ + OH^- \rightarrow R' - N \equiv C(OH) - R'' \quad \text{(LIX)}$$
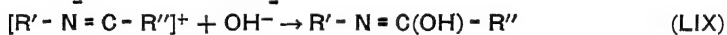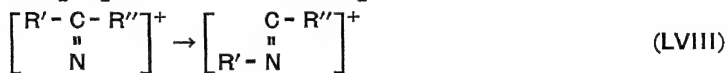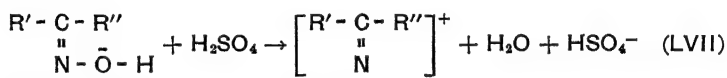
Instead of moderately concentrated sulfuric acid, in which the rate parallels the acidity function H_0,[62] phosphorus chlorides are frequently used as rearranging agents. These probably act by substituting the anion of a strong acid, *i.e.*, chloride ion or the ion of a phosphorus acid, for hydroxyl ion attached to nitrogen. The resulting ester then ionizes spontaneously or under the action of the solvent.

In some cases oxime esters of strong acids, such as the arylsulfonates and the picrates, may be isolated.[63] These rearrange when they are dissolved in solvents of the type that favors ionization, the faster, the more polar the medium. Thus the rate of rearrangement of benzophenone oxime picrate is 35 times as fast in dichlorethane as in benzene at 50°, and that in CCl₄ at 70° is 0.15 times that in benzene. In carbon tetrachloride, polar solvents produce a marked acceleration. At 81° the specific rate in the pure solvent is 4.75×10^{-5}. In 0.1M solutions of the

[61] CHAPMAN and HOWIS, *J. Chem. Soc.*, 806 (1933).

[62] HAMMETT and DEYRUP, *J. Am. Chem. Soc.*, **54**, 2721 (1932).

[63] KUHARA, MATSUMIYA, and MATSUNAMI, *C. A.*, **9**, 1613 (1915). CHAPMAN, *J. Chem. Soc.*, 1550 (1934).

following it is: CH_3CN, 9.9×10^{-5}; CH_3NO_2, 8.4×10^{-5}; acetone, 7.2×10^{-5}. Being polar substances, both the reactant and its rearrangement product also accelerate; hence, the order of the reaction is greater than one. The same effect is found in the solvolytic reaction of triphenylmethyl chloride.

Only the strongest acids form oxime esters that rearrange in this way. Although the picrate rearranges easily, the 2,4-dinitrophenolate fails to do so under the most favorable conditions. This effect together with the nature of the influence exerted by the solvent strongly supports the ionic mechanism, as does also the fact that the rearrangement of the picrate in the presence of the anions of another acid leads to the appearance of the latter in the final product.

The reaction shows the same kind of stereochemical specificity as the pinacol rearrangement (page 320). The oximes exist in two stereoisomeric forms, which differ in the sense that the hydroxyl group points either to the right or to the left. The configurations are known from the physical evidence of dipole moments and from chemical evidence involving ring opening and ring closure.[64] When the groups R' and R'' are not too different, the reactions of the isomers follow the course

$$
\begin{array}{ccc}
\text{R}' - \text{C} - \text{R}'' & & \text{R}' - \text{C} - \text{O} - \text{H} \\
\quad\ \| & \rightarrow & \quad\ \| \\
\text{H} - \text{O} - \text{N} & & \text{N} - \text{R}''
\end{array} \qquad \text{(LX)}
$$

$$
\begin{array}{ccc}
\text{R}' - \text{C} - \text{R}'' & & \text{H} - \text{O} - \text{C} - \text{R}'' \\
\quad\ \| & \rightarrow & \qquad\quad \| \\
\text{N} - \text{O} - \text{H} & & \text{R}' - \text{N}
\end{array} \qquad \text{(LXI)}
$$
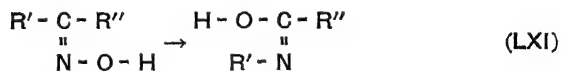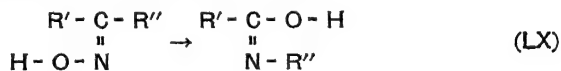
The group which shifts from carbon to nitrogen is the one which is in a position to attach itself to nitrogen on the side opposite to the original position of the hydroxyl, and the configuration of the nitrogen is inverted. As in so many cases of this sort, it is convenient to refer to the intermediate as an ion, but it is an ion that reacts further before it has lost the imprint of the structure from which it came.

Electron-attracting substituents retard, electron-repelling substituents accelerate the rearrangement of benzophenone oxime picrate.[65] When the substituent is in the migrating group, the

[64] Reviewed by Blatt, *Chem. Rev.*, **12**, 220 (1933).

[65] CHAPMAN and FIDLER, *J. Chem. Soc.*, 448 (1936).

relative rates in ethylene dichloride at 84° for *p*-chlor, unsub-
stituted, and *p*-methyl derivatives are as 0.20:1:8.0; when it is
in the stationary phenyl they are as 0.41:1:2.5; when both groups
are substituted they are as 0.09:1:28.   The last figures are nearly
enough the products of the first two sets.

The Hofmann Degradation and Related Rearrangements.—
Brombenzamides dissolve in aqueous alkali to form salts which
rearrange at a rate that is only slightly dependent upon the
concentration of sodium hydroxide.[66]   The probable mecha-
nism[66b] is

$$\left[C_6H_5 - \overset{\overset{\displaystyle \bar{O}\,'}{\|}}{C} - \bar{N} - \bar{B}r\,' \right]^{-} \rightarrow C_6H_5 - \overset{\overset{\displaystyle \bar{O}\,'}{\|}}{C} - \bar{N} + Br^{-} \qquad \text{(LXII)}$$

$$C_6H_5 - \overset{\overset{\displaystyle \bar{O}\,'}{\|}}{C} - \bar{N} \rightarrow C_6H_5 - \bar{N} \equiv C = \bar{O}\,' \qquad \text{(LXIII)}$$
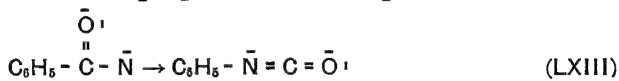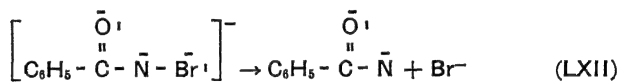
The shift of the phenyl group with its bonding pair from carbon
to a nitrogen that carries only six electrons is similar to the one
involved in the Beckmann rearrangement.   The phenyl iso-
cyanate reacts further in the aqueous medium according to known
reactions which yield primarily aniline and carbon dioxide and
secondarily diphenylurea.   The effect of meta and para substit-
uents in this reaction satisfies the usual linear free-energy rela-
tionship, the value of ρ being -2.50; ortho substituents lead to
relatively fast reaction.

The familiar Hofmann degradation involves reacting an acid
amide with alkaline hypobromite.   This no doubt forms a
bromamide that reacts according to equations (LXII) and
(LXIII).   The Curtius degradation of azides can be accounted
for by the following very similar process:

$$
\begin{array}{cccc}
R - C \equiv \bar{O}\,' & \quad C = \bar{O}\,' & \quad C = \bar{O}\,' & \\
\overset{|}{N}\,' & \quad R - \overset{|}{N}\,' & \quad R - \overset{|}{N}\,' & \\
\overset{|}{N}\,' & \rightarrow \quad \overset{|}{N}\,' & \rightarrow \quad \underset{\text{\tiny III}}{\bar{N}} & \quad \text{(LXIV)} \\
\overset{\|}{'N} & \quad '\overset{\|}{N} & \quad N & \\
\end{array}
$$
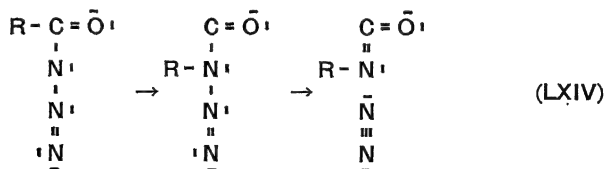
[66] (*a*) VAN DAM and ABERSON, *Rec. trav. chim.*, **19**, 318 (1900).   (*b*)
HAUSER and RENFROW, *J. Am. Chem. Soc.*, **59**, 121 (1937).

and the Schröter synthesis of diphenylketene by

$$
\begin{array}{ccc}
C_6H_5-C=\bar{O} & C=\bar{O}\,| & C=\bar{O}\,| \\
\quad| & \quad\| & \quad\| \\
C-C_6H_5 & C_6H_5-C-C_6H_5 & C_6H_5-C-C_6H_5 \\
\quad| \quad\rightarrow & \quad| \quad\rightarrow & \quad\bar{} \\
N\,| & N\,| & N \\
\quad\| & \quad\| & \quad\|\| \\
|\,N & |\,N & N \\
\underline{\ } & \underline{\ } & \underline{\ }
\end{array}
\qquad \text{(LXV)}
$$
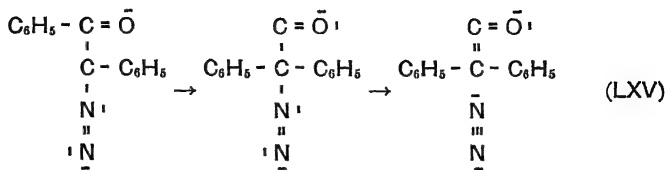
Substances of the type C_6H_5CO—NH—O—CO—C_6H_5 are rearranged by bases to the same products as the brombenzamides.[67] The process is favored by electron-attracting substituents in the right-hand phenyl and retarded by the same substituents when they are in the left-hand phenyl (page 190). These effects correspond to a key process of the same type as reaction (LXII).

In the rearrangements of the optically active substances (R)

$$
\begin{array}{l}
C_6H_5CH_2 \quad\quad H \\
\quad\quad\diagdown\;\diagup \\
\quad\quad\quad C \\
\quad\quad\diagup\;\diagdown \\
CH_3 \quad\quad C-N=N=N \\
\quad\quad\quad\quad\| \\
\quad\quad\quad\quad O \\
\quad\quad\quad (R)
\end{array}
\qquad
\begin{array}{l}
C_6H_5CH_2 \quad\quad H \\
\quad\quad\diagdown\;\diagup \\
\quad\quad\quad C \\
\quad\quad\diagup\;\diagdown \\
CH_3 \quad\quad C-NH-O-CO-CH_3 \\
\quad\quad\quad\quad\| \\
\quad\quad\quad\quad O \\
\quad\quad\quad\quad\quad\quad (S) \\
\quad\quad\quad\quad\quad C_6H_5-CH_2 \quad\quad H \\
\quad\quad\quad\quad\quad\quad\quad\diagdown\;\diagup \\
\quad\quad\quad\quad\quad\quad\quad\quad C \\
\quad\quad\quad\quad\quad\quad\quad\diagup\;\diagdown \\
\quad\quad\quad\quad\quad CH_3 \quad\quad C-NH_2 \\
\quad\quad\quad\quad\quad\quad\quad\quad\quad\| \\
\quad\quad\quad\quad\quad\quad\quad\quad\quad O \\
\quad\quad\quad\quad\quad\quad\quad\quad (T)
\end{array}
$$
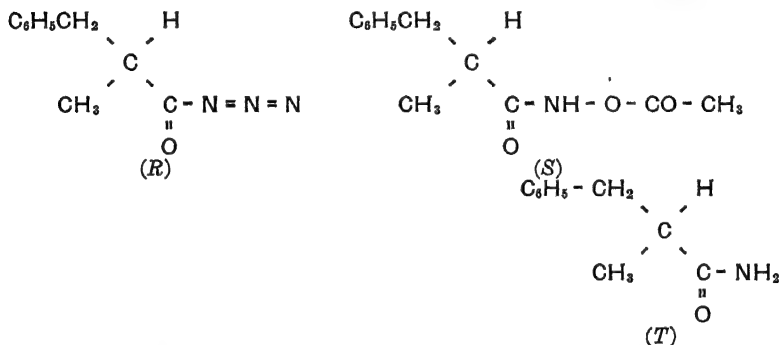
and (S) and the Hofmann degradation of the active amide (T), the products are all active and have the same sign and magnitude of rotation. It seems, therefore, improbable that much racemization has occurred, but it is not known whether the configuration of the migrating group has been inverted or not.[68]

Rearrangements Involving the Shift of a Positive Group.—The diazoamino rearrangement

$$
C_6H_5-NH-N=N-C_6H_5 \rightarrow pH_2NC_6H_4-N=N-C_6H_5 \qquad \text{(LXVI)}
$$

[67] Renfrow and Hauser, *J. Am. Chem. Soc.*, **59**, 2309 (1937).
[68] Jones and Wallis, *J. Am. Chem. Soc.*, **48**, 169 (1926). Wallis and Nagel, *ibid.*, **53**, 2787 (1931). Wallis and Dripps, *ibid.*, **55**, 1701 (1933). Wallis and Moyer, *ibid.*, **55**, 2598 (1933).

is most satisfactorily carried out by dissolving the reactant in aniline along with aniline hydrochloride, the anilinium ion of the latter being an acid catalyst (page 286). The reaction is external rather than internal and involves a dissociation followed by recombination. Thus the reaction of $CH_3C_6H_4NH—N{=}N—C_6H_4CH_3$ in the solvent aniline leads chiefly to $H_2NC_6H_4—N{=}N—C_6H_4CH_3$.[69] The following is, therefore, a satisfactory mechanism

$$C_6H_5 - \bar{N} - \bar{N} = \bar{N} - C_6H_5 + BH^+ \rightleftharpoons \left[C_6H_5 - \overset{\overset{H}{|}}{N} - \bar{N} = \bar{N} - C_6H_5 \right]^+ + B \quad \text{(LXVII)}$$

$$\left[C_6H_5 - \overset{\overset{H}{|}}{\underset{\underset{H}{|}}{N}} - \bar{N} = \bar{N} - C_6H_5 \right]^+ \rightleftharpoons C_6H_5\bar{N}H_2 + [\textrm{·}\,N \equiv N - C_6H_5]^+ \quad \text{(LXVIII)}$$
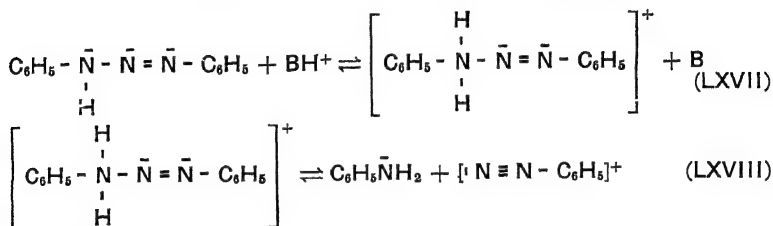
The benzenediazonium ion then couples with an aniline molecule in the para position. The reaction can be made to take place in water, but the yield is poor because the formation of phenol and other reactions of the diazonium ion have rates comparable with that of the coupling. In the presence of the readily coupling β-naphthol, diazoaminobenzene in water solution gives a 90 per cent yield of benzeneazo-β-naphthol and aniline. Using aniline as a solvent for the reaction simply increases the rate of the coupling relative to that of the side reactions.

Aminoazobenzene is obviously more stable than diazoaminobenzene; yet its rate of formation from aniline and benzenediazonium ion is slower. This is another example of the principle that parallelism between rate and equilibrium cannot be counted on when the nature of the reacting groups differs. Here one reaction involves the formation of a nitrogen-carbon link, the other the formation of a nitrogen-nitrogen link.

The rearrangement of *N*-alkylanilinium salt to nuclear alkylated aniline probably takes a similar course with the carbonium ion of the migrating alkyl as the intermediate.[70] The acid-catalyzed rearrangement of alkyl phenol ethers to nuclear alkylated phenols appears to be of the same sort and is certainly

[69] NIETZKI, *Ber.*, **10**, 662 (1877). ROSENHAUER and UNGER, *ibid.*, **61**, 392 (1928). KIDD, *J. Org. Chem.*, **2**, 198 (1937).

[70] HICKINBOTTOM, *J. Chem. Soc.*, 1700 (1934).

external in some if not all cases, since *p*-ethyl anisole is formed when ethyl phenyl ether rearranges with anisole as the solvent.[71] With longer alkyl groups the typical rearrangements of a carbonium ion occur, thus phenyl-*s*-butyl ether yields *t*-butylphenol. When the alkyl group is asymmetric, the rearranged material is optically active, which is not incompatible with the carbonium-ion mechanism.[72] The rearrangement of phenyl allyl ethers may possibly involve an internal ring formation, but the evidence for this is incomplete.

The acid-catalyzed benzidine rearrangement

$$C_6H_5 - NH - NH - C_6H_5 \rightarrow H_2NC_6H_4 - C_6H_4NH_2 \qquad (LXIX)$$

appears to be internal since a mixture of 2,2′-dimethoxybenzidine and 2,2′-diethoxybenzidine, which rearrange at comparable rates, yields none of the 2-methoxy-2′-ethoxydiphenyl which should be formed if a rupture of the reactant into fragments were involved.[73] The internal reaction in this case may be connected with the possibility of configurations in which the para positions of the two rings are close together.

In the rearrangement

(LXX)
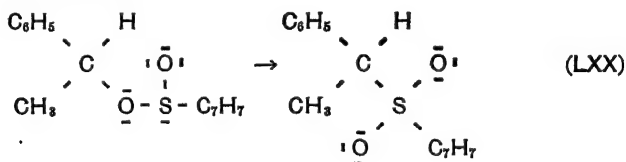
optically active sulfinate yields largely but not always completely racemized sulfone.[74] The configuration of the alkyl group appears to be retained. This is contrary to all experience if the reaction involves a rupture into carbonium and sulfinate ions; it is intelligible if the shift is an internal one.

The N-Halogenacylanilide Rearrangement.—The rearrangement of *N*-chloracetanilide in aqueous solution has a rate that is proportional to the product of the activities of oxonium and chloride ions or, what amounts to the same thing, to the activity of

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[71] SHORT and STEWART, *J. Chem. Soc.*, 553 (1929).

[72] SPRUNG and WALLIS, *J. Am. Chem. Soc.*, **56**, 1715 (1934).

[73] INGOLD and REID, *J. Chem. Soc.*, 984 (1933).

[74] ARCUS, BALFE, and KENYON, *J. Chem. Soc.*, 485 (1938).

molecular HCl (page 277).   The reaction is specifically dependent upon the presence of chloride ion, other acids than hydrochloric having relatively little effect.   When it is carried out in the presence of radioactive chloride ion, the rate of entrance of radioactivity into the organic materials is greater than the rate of rearrangement.[75]   These effects are consistent with the mechanism

$$C_6H_5 - \bar{N} \overset{\overset{\displaystyle \bar{C}l}{|}}{\underset{\underset{\displaystyle {}^|O}{C - CH_3}}{}} \ \ + OH_3^+ + Cl^- \rightleftharpoons C_6H_5 - \bar{N} \overset{\overset{\displaystyle H}{|}}{\underset{\underset{\displaystyle {}^|O}{C - CH_3}}{}}$$

$$+ H_2O + {}^{\centerdot}\bar{C}l - \bar{C}l^{\centerdot} \quad (LXXI)$$

$$C_6H_5 - NH - CO - CH_3 + Cl_2 \rightarrow Cl - C_6H_4NH - CO - CH_3 + HCl \quad (LXXII)$$
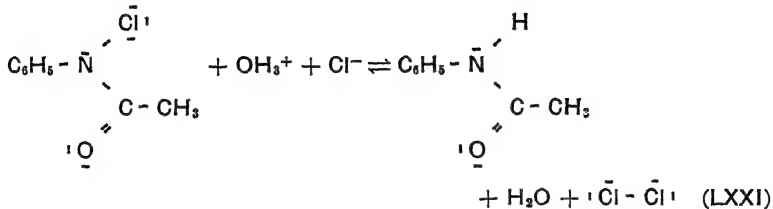
with the second step rate determining.   The first step probably involves the reversible addition of a proton to the unshared pair of the nitrogen, which so increases the positivity of the chlorine that it becomes easily transferred to a chloride ion. The rearrangement is far from clean, 30 to 75 per cent of the reactant being converted to unidentified products other than p-chloracetanilide.[75b]

The analogous rearrangement of N-bromacetanilide, on the other hand, cannot have Br_2 as an intermediate because the concentration of bromine can be shown to be too small, the rate of reaction of bromine with acetanilide having been independently determined.[76]   The intermediate may very well be the ion Br^+.

[75] (a) OLSON, HALFORD, and HORNEL, J. Am. Chem. Soc., 59, 1613 (1937). (b) OLSON and HORNEL, J. Org. Chem., 3, 76 (1938).

[76] BELL, J. Chem. Soc., 1154 (1936).

CHAPTER XI

CARBONYL-ADDITION REACTIONS

Catalysis in Carbonyl-addition Reactions.—Although the typical addition reaction of the carbonyl group involves the attachment of a nucleophilic group to the carbon of the carbonyl, very few reactions exhibiting the simple kinetics of this process have been investigated. Lapworth's evidence (page 152) that the cyanhydrine reaction has as a rate-determining step the process

$$\begin{array}{c} R \\ \diagdown \\ \diagup \\ R \end{array} C = \underline{O}\,' + CN^- \rightarrow \left[\begin{array}{cc} R & \bar{O}\,' \\ \diagdown & \diagup \\ C & \\ \diagup & \diagdown \\ R & CN \end{array} \right]^- \tag{I}$$
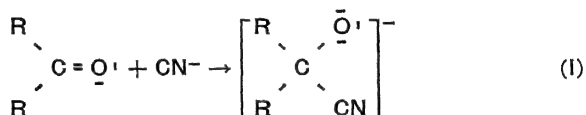
is convincing even though it is qualitative. The second-order reactions of carbon dioxide with hydroxyl and alkyloxy ions,[1] e.g.,

$$'\bar{O} = C = \bar{O}\,' + ['\underline{O} - H]^- \rightarrow \left[\begin{array}{c} \bar{O}\,' \\ \diagup \\ '\bar{O} = C \\ \diagdown \\ \underline{O} - H \end{array} \right]^- \tag{II}$$
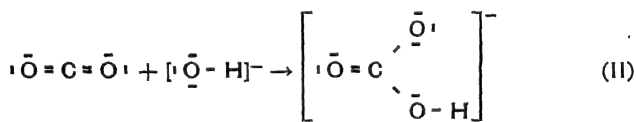
are of this type as are the initial steps in the hydroxyl-ion catalyzed oxygen exchange on ketones (page 242) and the benzilic acid rearrangement (page 321). A most important example is the reaction with the Grignard reagent, which involves a similar addition of the carbanion of the reagent to the carbonyl carbon

$$\begin{array}{c} R \\ \diagdown \\ \diagup \\ R \end{array} C = \bar{O}\,' + R' - Mg^+ \rightarrow \left[\begin{array}{cc} R & R' \\ \diagdown & \diagup \\ C & \\ \diagup & \diagdown \\ R & \underline{O}\,' \end{array} \right]^- + Mg^{++} \tag{III}$$
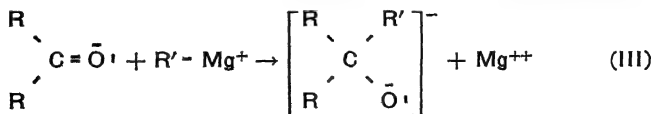
More generally, the kinetics of these reactions show complications which result from the fact that both reactants are bases.

[1] FAURHOLT, *Z. physik. Chem.*, **126**, 72; 85; 211; 227 (1927).

in which c_S is the stoichiometric concentration of semicarbazide (base plus conjugate acid), it follows that

$$k_+ = \frac{v}{[AO]c_S} = \frac{K_R}{K_R + [OH_3^+]}\sum_i k_i[HA_i] \qquad (5)$$

If only one acid other than oxonium ion is present, this reduces to

$$k_+ = \frac{K_R}{K_R + [OH_3^+]}\{k_A[HA] + k_H[OH_3^+]\} \qquad (6)$$

and by use of

$$[OH_3^+] = K_A\frac{[HA]}{[A^-]}$$

to

$$k_+ = \frac{K_R}{K_R + K_A\frac{[HA]}{[A^-]}}\left\{k_A[HA] + k_H K_A\frac{[HA]}{[A^-]}\right\} \qquad (7)$$

According to equation (7) the specific rate k increases indefinitely (the derivative $\partial k/\partial[HA]$ is always positive) when the concentration of the acid HA is increased while the concentration of the conjugate base A^- is held constant. A more usual experimental procedure, however, is to study the reaction in a series of buffer solutions for which the sum $[HA] + [A^-]$ is a constant. For this condition equation (7) predicts a maximum rate at a pH that is a complicated function of the rate and equilibrium constants involved. If the further condition is applied that the term $k_H[OH_3^+]$ of equation (6) may be neglected compared with $k_A[HA]$, if therefore catalysis by oxonium ion is negligible compared with that by the acid HA, the condition for the maximum rate of reaction reduces to

$$[OH_3^+] = \sqrt{K_R K_A} \qquad (8)$$

and the maximum rate is observed when the concentration of oxonium ion is the geometric mean of the acidity constants of the catalyst acid and the conjugate acid of semicarbazide. Since the range of acidities that can be established and maintained by buffer solutions of a given acid is limited to one pH unit or so on either side of a value of pH equal to the pK_a of the·

acid, the maximum will be observed experimentally only when the catalyst acid does not differ too widely in strength from the semicarbazide conjugate acid.

Table I.—Rate of Formation of Acetone Semicarbazone[2a]

Buffer	pH	k
Citrate.....................................	2.84	0.0188
Acetate..	4.00	0.071
Acetate.....................................	4.52	0.091
Acetate.....................................	4.84	0.088
Phosphate................................	5.84	0.095
Phosphate................................	7.00	0.034

The concordance of these conclusions with the experimental data is demonstrated in Table I, which presents data on the formation of acetone semicarbazone in water at 0.1°. The rate in acetate buffers goes through a maximum at a pH close to the value 4.6 predicted from equation (8) and the values $pK_R = 4.40$ and $pK_A = 4.78$. The rate is very different in phosphate buffers and in acetate buffers of the same pH, a characteristic general acid catalysis phenomenon, and general acid catalysis is further demonstrated by the fact that the rate of formation of furfural semicarbazone in a series of acetate buffers of pH $= 4.4$ increases by a factor of 1.8 when the buffer concentration is increased from 0.030 to 0.069M. The predicted maximum for phosphate buffers lies at 5.5, which is outside the practicable range of these buffers.

From the practical point of view, the highest rate is obtained by using the largest possible concentration of an acid, the acidity constant of which is approximately the same as that of the conjugate acid of semicarbazide, together with sufficient of the base conjugate to the catalyst to make the pH nearly equal to pK_R. An acetic acid-acetate buffer fits these specifications excellently.

The effect of the structure of the carbonyl compound upon the rate of semicarbazone formation has already been listed (page 211). As in other cases where such unrestricted changes in structure are involved, these figures must not be assigned very general significance. The ratio of the rates of reaction of two carbonyl compounds varies with the medium in which the reaction occurs and with the catalyzing acid, and such specific

effects may even lead to a reversal of the order of reactivities. Thus the rate of reaction of acetone is four times as large as that of *o*-nitrobenzaldehyde in an acetate buffer in a methyl cellosolve-water medium and only one-third as large in a chloracetate buffer in the same medium. This means merely that the x of the Brønsted catalytic equation has very different values for the different carbonyl compounds. The situation is typical of the difficulties that confront the attempt to translate the skilled organic chemist's feel for structural effects into quantitative or even into unambiguous qualitative relationships.

The Mechanism of the Semicarbazone Reaction.—Since the carbon-nitrogen linkage in the semicarbazone is formed by an electron pair contributed by the semicarbazide, the catalysis must depend upon an attack by the acid on the carbonyl compound. Such an attack must decrease the electron density on the carbonyl carbon and favor the formation of the carbon-nitrogen bond; an attack on the semicarbazide would decrease the electron density on the nitrogen, which is unfavorable to reaction. If the reaction follows the steps

$$R_2C \! = \! O + HA \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} [R_2C \text{-} O \text{-} H]^+ + A^- \qquad (VI)$$

$$[R_2C \text{-} O \text{-} H]^+ + H_2N \text{-} NH \text{-} CONH_2 \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} \begin{bmatrix} H \text{-} O & H \\ & | & | \\ R_2C \text{-} & N \text{-} NH \text{-} CONH_2 \\ & | & \\ & H & \end{bmatrix}^+ \quad (VII)$$

$$[R_2C(OH) \text{-} NH_2 \text{-} NH \text{-} CONH_2]^+ + A^- \overset{k_3}{\rightarrow} \\ R_2C(OH) \text{-} NH \text{-} NH \text{-} CONH_2 + HA \quad (VIII)$$
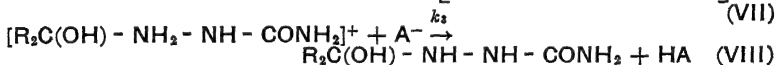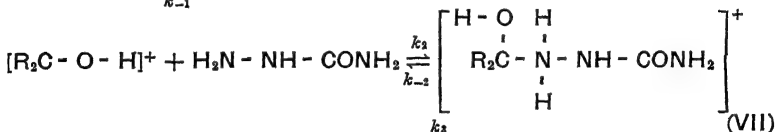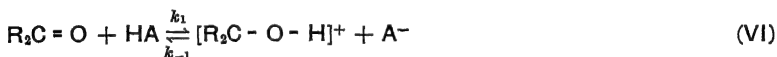
followed by a rapid dehydration of the semicarbazone hydrate, either reaction (VIII) or some later proton transfer must be rate determining. If reaction (VI) were determining, the rate would be independent of the concentration of semicarbazide; if reaction (VII) were determining, the rate equation would be

$$v = \frac{k_1 k_2}{k_{-1}}[AO][H_2NB]\frac{[HA]}{[A^-]} \qquad (9)$$

and the reaction would show specific oxonium-ion catalysis. If reaction (VIII) is rate determining, the rate equation becomes

$$v = \frac{k_1 k_2 k_3}{k_{-1} k_{-2}}[AO][H_2NB][HA] = K_1 K_2 k_3[AO][H_2NB][HA] \quad (10)$$

in agreement with experiment. The same dependence of rate on concentration follows if the reaction depends upon a reversible hydrogen bonding of acid and carbonyl compound

$$R_2C = O + HA \rightleftharpoons R_2C = O\text{---}H\text{-}A \qquad (IX)$$
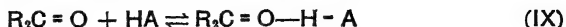
or less probably if the reaction is truly termolecular and involves a three-body collision. In terms of the transition-state theory the distinction between the mechanism of reactions (VI), (VII), and (VIIII) and the alternatives reduces to the question of whether the transition state (*A*) or (*B*) is the more probable.
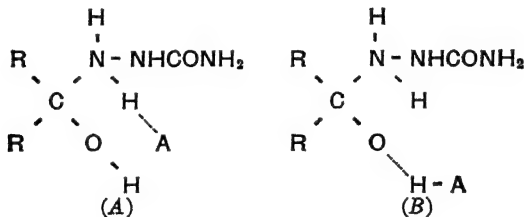
The kinetics and presumably the mechanisms of reaction of the other classical carbonyl reagents are similar to those of semicarbazide, although they have been less completely investigated. The formation of oximes shows an optimum pH when measured with ordinary buffer systems, the rate decreasing at both higher and lower acidities.[3] In strongly alkaline solutions the rate increases again, presumably because of the formation of $[H_2NO]^-$, which should be a more active nucleophilic reagent than H_2NOH.[4] The phenylhydrazone and osazone reactions of sugars have rates that depend upon the nature and concentration of the buffer solution in which the reaction occurs, even when the pH is constant.[5] This fact demonstrates the presence of a general acid catalysis.

The Equilibrium of the Semicarbazone Reaction.—The semicarbazone formation is reversible and comes to an equilibrium the composition of which is markedly affected by the acidity of the solution because semicarbazide and the semicarbazone are both bases. If the acidity constants of semicarbazide and of the semicarbazone ANB are defined by the equations

[3] ÖLANDER, *Z. physik. Chem.*, **129**, 1 (1927).

[4] BARRETT and LAPWORTH, *J. Chem. Soc.*, **93**, 85 (1908). ACREE and JOHNSON, *Am. Chem. J.*, **38**, 308 (1907).

[5] ARDAGH and RUTHERFORD, *J. Am. Chem. Soc.*, **57**, 1085 (1935).

$$K_R = \frac{[BNH_2][OH_3^+]}{[BNH_3^+]} \tag{11}$$

$$K_C = \frac{[ANB][OH_3^+]}{[ANBH^+]} \tag{12}$$

and the true equilibrium constant for the semicarbazone formation by

$$K_0 = \frac{[ANB]}{[AO][BNH_2]} \tag{13}$$

then the apparent constant

$$K = \frac{[ANB] + [ANBH^+]}{\{[BNH_2] + [BNH_3^+]\}[AO]} \tag{14}$$

is easily shown to be given by

$$K = K_0 \frac{1 + \dfrac{[OH_3^+]}{K_C}}{1 + \dfrac{[OH_3^+]}{K_R}} \tag{15}$$

This equation agrees satisfactorily with the experimental observations, as indeed it must if the activity coefficients involved are reasonably constant. K varies from a value equal to K_0 at low acidities to the considerably smaller value $K_0 K_R / K_C$ at high ones. Table II lists values of the various equilibrium constants in

TABLE II.—EQUILIBRIUM IN SEMICARBAZONE FORMATION AND SIMILAR REACTIONS AT 25°[2a]

Substance	$10^{-3}K_0$	K_C	$10^3 K_R$	$K_0 K_R / K_C$
Furfural semicarbazone..........	130	0.036	0.22	800
Acetaldehyde semicarbazone......	48	0.078	0.22	135
Benzaldehyde semicarbazone.....	330	0.111	0.22	660
Pyruvic acid semicarbazone......	200	0.258	0.22	170
Acetone semicarbazone..........	0.31	0.046	0.22	1.5
Acetone oxime.................	1080	0.012	0.00080	72
Acetone phenylhydrazone........	0.6	.....	0.0061	

aqueous solution at 25°. Only in the case of acetone semicarbazone and probably in that of acetone phenylhydrazone is the extent of reaction small even in acid solution.

The kinetics of the hydrolysis of a semicarbazone follow from equation (15) for the equilibrium and equation (6) for the rate of

formation together with the relation $K = k_+/k_-$. These lead to

$$k_- = \frac{K_C}{K_0\{K_C + [OH_3^+]\}}\{k_H[HA] + k_H[OH_3^+]\} \qquad (16)$$

The reaction must, therefore, show general acid catalysis and an optimum rate at a pH that bears the same relation to K_C as the optimum rate of formation does to K_R. The transition state must be the same for forward and reverse reactions, and instead of A or B might rather obviously be (C).

$$\begin{array}{cc} R & H\cdots A \\ | & | \\ R-C-N-NHCONH_2 \\ | & \\ H-O-H \\ & (C) \end{array}$$
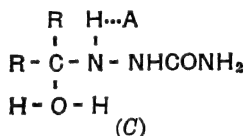
Addition Reactions of Quinones.—These are 1:4 additions to a conjugated system. The reaction with HCl has a rate in methanol that varies approximately as the square of the concentration of HCl and probably exactly as the product of the activities of oxonium and chloride ions.[6] The probable mechanism involves the reversible addition of a proton and the rate-determining attachment of a chloride ion

$$(X)$$

$$(XI)$$
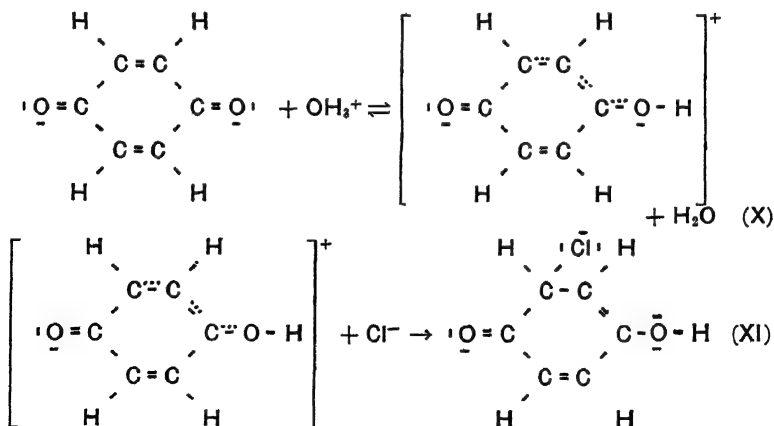
followed by an enolization to chlorhydroquinone.

[6] EBERT, *Z. Elektrochem.*, **31**, 113 (1925).

The Mutarotation of Glucose.—This depends upon the reversal of a carbonyl-addition reaction. The reaction consists in the reversible interconversion of one stereoisomeric form of glucose into another which differs only in the configuration of the carbon atom marked with a star in formula (D)

(D)
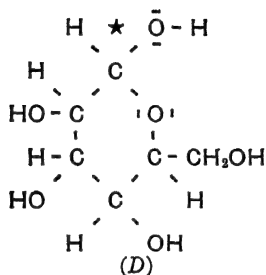
and requires, therefore, the rupture and reestablishment in an inverted configuration of one of its linkages. This link cannot be the one to hydrogen because the mutarotation is not accompanied by the replacement of this hydrogen by deuterium when the reaction takes place in D_2O;[7] it must therefore be that to oxygen. In view of the general acid and general base catalysis the only reasonable mechanisms are the following: for the acid catalysis the mobile and reversible addition of a proton to the ether oxygen followed by a rate-determining reaction with a base

(XII)
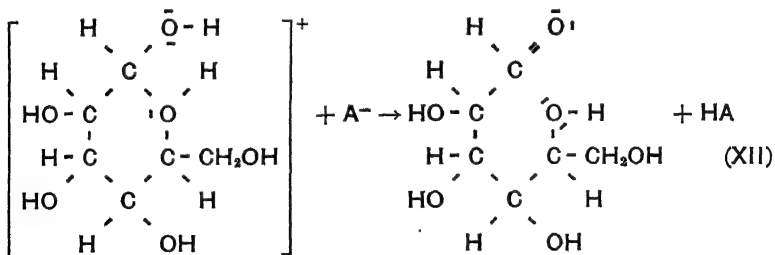
for the base catalysis the mobile and reversible removal of a proton, followed by a rate-determining reaction with an acid

[7] FREDENHAGEN and BONHOEFFER, *Z. physik. Chem.*, **A181**, 392 (1938).

$$\left[\begin{array}{c} H \quad \bar{O}\text{'} \\ H \quad C \\ HO-C \quad \text{'}O\text{'} \\ H-C \quad C-CH_2OH \\ HO \quad C \quad H \\ H \quad OH \end{array}\right]^{-} + BH^{+} \rightarrow \begin{array}{c} H \quad \bar{O}\text{'} \\ H \quad C \\ HO-C \quad \text{'}O-H \\ H-C \quad C-CH_2OH \\ HO \quad C \quad H \\ H \quad OH \end{array} + B \qquad (XIII)$$
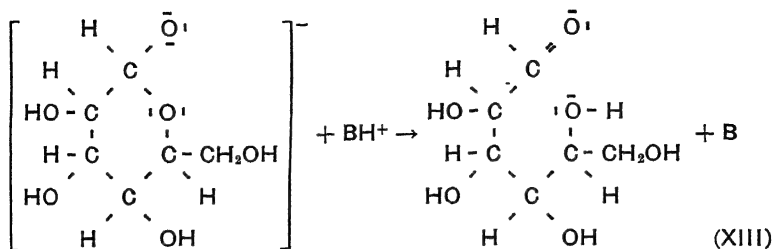
In either case the reversion of the aldehydic form of the sugar to the ring form may take place in either configuration of the aldehydic carbon, and this accounts for the change in rotation. The driving force necessary for the rupture of the ether linkage must be attributed to the incipient formation of the carbonyl group as must also the fact that this reaction, unlike others involving ether linkages, shows a base as well as an acid catalysis.

The mutarotation requires an acid as well as a base; it involves the addition as well as the loss of a proton. That neither alone is sufficient is demonstrated in the case of tetramethylglucose by the fact that mutarotation is not observed in the moderately acid but very weakly basic solvent cresol, nor in the basic but not acidic solvent pyridine, but is rapid in a mixture of the two solvents.[8] This does not, however, prove that the attack of the acid and the base must be simultaneous; either the addition or the loss of the proton may become the bottleneck according as the acidity or the basicity of the medium is low and regardless of the sequence of the operations.[9]

The hydrolysis of dimeric dihydroxyacetone (*E*) likewise involves the rupture of a cyclic hemiacetal and also shows general

$$\begin{array}{c} HOCH_2 \quad O-CH_2 \quad OH \\ C \qquad C \\ HO \quad CH_2-O \quad CH_2OH \\ (E) \end{array}$$
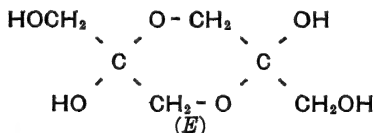
acid and general base catalysis.[10]

The Reactions of Cyanamide.—These are typical of the addition reactions of the C≡N double bond and have been studied in

[8] Lowry and Richards, *J. Chem. Soc.*, **127**, 1385 (1925).

[9] Pedersen, Dis., Copenhagen 1932; *J. Phys. Chem.*, **38**, 581 (1934).

[10] Bell and Baughan, *J. Chem. Soc.*, 1947 (1937).

a most illuminating fashion.[11] Cyanamide, $HN{=}C{=}NH$, is a weak acid the ionization constant[12] of which at 50° is 2.01×10^{-10}. It may be hydrolyzed to urea by a reaction that is catalyzed both by strong acids (page 274) and by strong bases. It is polymerized to dicyandiamide by a reaction that is second order in cyanamide and shows a sharp maximum in rate at a pH of 9.7, with the rate dropping off rapidly in more and in less alkaline solutions. These results are consistent with the kinetic law

$$v = k_0[\text{HNCNH}][\text{HNCN}^-] \tag{17}$$

If c is the stoichiometric concentration of cyanamide

$$c = [\text{HNCNH}] + [\text{HNCN}^-] \tag{18}$$

and K the acidity constant of cyanamide it is easily shown that the specific rate $k = v/c^2$ is given by

$$k = k_0 \frac{K[\text{OH}_3^+]}{\{K + [\text{OH}_3^+]\}^2} \tag{19}$$

This function has a maximum when $K = [\text{OH}_3^+]$, *i.e.*, when

$$\text{pH} = \text{p}K = 9.7 \tag{20}$$

in agreement with the experimental results. Table III shows the correspondence of the experimental values of k with those predicted from equation (19).

TABLE III.—OBSERVED AND CALCULATED SPECIFIC RATES IN CYANAMIDE POLYMERIZATION[11]

pH	9.0	9.6	10.5	11.4
$10^5 k$ (obs.)	5.8	9.2	5.8	0.86
$10^5 k$ (calc.)	5.8	10.6	5.8	0.86

The reaction mechanism can be obviously and satisfactorily accounted for as an addition of the nucleophilic anion to the carbon end of the $C{=}N$ system

[11] BUCHANAN and BARSKY, *J. Am. Chem. Soc.*, **52**, 195 (1930). BARSKY and BUCHANAN, *ibid.*, **53**, 1270 (1931). BARSKY, *Chemie & Industrie*, **28**, 1032 (1932).

[12] KAMAYAMA, *Trans. Electrochemical Soc.*, **40**, 131 (1921).

$$H - \bar{N} = C = \bar{N} - H + [\, \cdot \bar{N} = C = \bar{N} - H]^- \rightarrow \left[\begin{array}{c} H - \underset{\underset{|}{}}{\bar{N}} - C = \bar{N} - H \\ \cdot N = C = \bar{N} - H \end{array} \right]^- \quad \text{(XIV)}$$
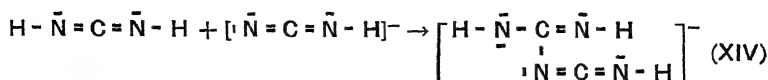
forming the conjugate base of the polymer.

The base-catalyzed hydrolysis of cyanamide to urea can be observed only in solutions so alkaline that the polymerization rate is small. Under these conditions the rate is independent of hydroxyl-ion concentration. This is nevertheless consistent with an addition of hydroxyl ion to neutral cyanamide as the rate-determining step

$$H - \bar{N} = C = \bar{N} - H + [\, \cdot \underset{-}{\bar{O}} - H]^- \rightarrow \left[\begin{array}{c} H - \underset{\underset{|}{}}{\bar{N}} - C = \bar{N} - H \\ \cdot \underset{-}{O} - H \end{array} \right]^- \quad \text{(XV)}$$
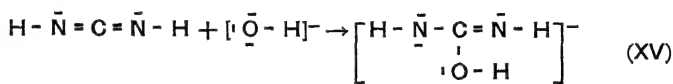
and the conjugate base of isourea as its product. The rate equation for this mechanism is

$$v = k[\text{HNCNH}][\text{OH}^-] = k\frac{c[\text{OH}_3^+]}{K + [\text{OH}_3^+]}[\text{OH}^-]$$

$$= \frac{kK_w c}{K + [\text{OH}_3^+]} \quad (21)$$

This becomes independent of acidity in strongly alkaline solutions because $[\text{OH}_3^+] \ll K$. The situation arises from the fact that the conversion of cyanamide to the conjugate base is nearly complete, and the concentration of neutral cyanamide varies inversely as the hydroxyl-ion concentration. The probable intermediates in the acid-catalyzed hydrolysis are (*F*), (*G*), and (*H*).

$$\left[\begin{array}{c} H - \bar{N} = C - N{<}_{}^{H} \\ H \end{array} \right]^+ \qquad \left[\begin{array}{c} H - \bar{N} = C - \bar{N} - H \\ H - \underset{|}{O} - H \quad H \end{array} \right]^+ \qquad \begin{array}{c} H - \bar{N} = C - \bar{N}{<}^{H} \\ \cdot \underset{-}{O} - H \quad H \end{array}$$

$$(F) \qquad\qquad\qquad (G) \qquad\qquad\qquad (\bar{H})$$
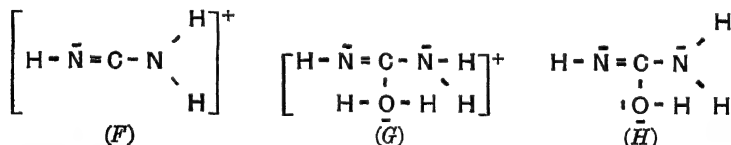
The reaction of hydrogen sulfide with cyanamide to form thiourea shows kinetics which indicate that it involves the addition of HS^- to neutral cyanamide. The rate equation for such a process is

$$v = \frac{kc_C c_S K_S[\text{OH}_3^+]}{\{K_C + [\text{OH}_3^+]\}\{K_S + [\text{OH}_3^+]\}} \quad (22)$$

with c_C and c_S the stoichiometric concentrations of cyanamide and hydrogen sulfide and K_C and K_S the acidity constants of the same substances. The rate has a sharp maximum when

$$[OH_3^+] = \sqrt{K_C K_S} \tag{23}$$

Since hydrogen sulfide is a considerably stronger acid than cyanamide ($pK = 7$ at $25°$), the maximum appears in a considerably more acid solution than does that for the polymerization. Consequently, it is possible to make the technically desirable synthesis of thiourea predominate over the undesired polymerization.

On the other hand, the addition of cyanide ion to cyanamide to form a product, presumably $HN{=}C(CN){-}NH_2$, that can be hydrolyzed by acids to oxalic acid cannot be favored in competition with the polymerization by adjustment of the pH. This is because the ionization constant of HCN ($pK = 9.14$ at $25°$) is so nearly the same as that of cyanamide that the addition and the polymerization have nearly the same dependence on acidity.

The Decomposition of Formocholine Chloride.[13]—The reaction

$$[(CH_3)_3NCH_2OH]^+ \rightarrow (CH_3)_3NH^+ + CH_2O \tag{XVI}$$

reverses a carbonyl-addition reaction. The rate varies inversely as the concentration of oxonium ion in citrate buffers at pH's in the neighborhood of 2 or 3 and is very rapid in alkaline solutions. At $25°$ the equation

$$\log k = -5.795 + pH \tag{24}$$

is satisfied by the trimethyl derivative and the equation

$$\log k = -4.991 + pH \tag{25}$$

by the triethyl derivative. There appears to be no general base catalysis, for threefold dilution of the buffer changes the rate only 2 per cent. A satisfactory mechanism involves the reversible removal of a proton, followed by a first-order rupture of the C—N bond

[13] STEWART and KUNG, *J. Am. Chem. Soc.*, **55**, 4813 (1933).

$$\underset{\underset{CH_3}{|}}{\overset{\overset{CH_3}{|}}{CH_3-N}}\underset{\underset{H}{|}}{\overset{\overset{H}{|}}{-C}}-\overset{..}{\underset{..}{O}}: \rightarrow CH_3-\underset{\underset{CH_3}{|}}{\overset{\overset{CH_3}{|}}{N}}: + \underset{\underset{H}{}}{\overset{\overset{H}{}}{C}}=\overset{..}{O}: \qquad (XVII)$$
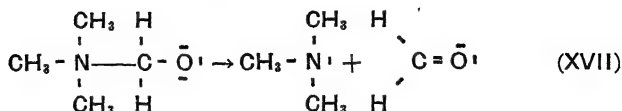
The normally firm bond is easily ruptured because of the incipient formation in the transition state of the C=O bond.

The closely related reaction[14]

$$\underset{\underset{\underset{H}{\diagup}}{\overset{R}{\diagdown}}\ \underset{\overset{\diagdown}{SO_3}}{\overset{C}{\diagup}}}{\overset{\overset{\underset{H}{\diagup}}{\overset{R}{\diagdown}}\ \overset{\overset{\diagup}{H}}{N}\ H}{}} \rightleftharpoons \underset{\overset{R}{\diagup}}{\overset{\overset{R}{\diagdown}}{N}} = CH_2^+ + HSO_3^- \qquad (XVIII)$$
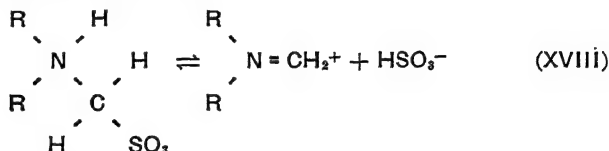
is reversible and has a small equilibrium constant. In the presence of iodine, bromine, or hydrogen peroxide the sulfite is rapidly and irreversibly oxidized, the reverse reaction is suppressed, and reaction (XVIII) becomes the rate-determining step of the oxidation process, the rate of which is independent both of the nature and of the concentration of the oxidizing agent. The rate of this reaction decreases with increasing acidity up to a pH of 1 beyond which there is little effect. At 30° the rates for various R's are as follows: methyl 0.00103; ethyl, 0.00271; *n*-propyl, 0.00923; *i*-propyl, very fast; whereas that for the piperidine derivative is 0.000554, showing a large and specific effect of ring closure.

The Aminonitrile Reaction.[15]—Acetone cyanhydrine and diethylamine react in acetone at a rate which is strictly proportional to the product of the concentrations of cyanhydrine and of amine and which shows a pronounced linear acceleration by tertiary amines. In ethyl alcohol, the rate is small unless acetone is added; when acetone is added, it is proportional to the product of the concentrations of acetone and amine and independent of the concentration of cyanhydrine. Except for the catalysis by tertiary amines, these effects are accounted for by the series of reactions

$$(CH_3)_2C(OH)CN \rightleftharpoons (CH_3)_2C=O + HCN \qquad (XIX)$$
$$(CH_3)_2CO + R_2NH \rightleftharpoons (CH_3)_2C(OH)NR_2 \qquad (XX)$$
$$(CH_3)_2C(OH)NR_2 + HCN \rightarrow (CH_3)_2C(CN)NR_2 + H_2O \qquad (XXI)$$
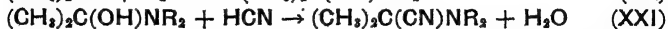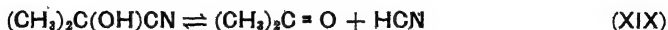
[14] STEWART and BRADLEY, *J. Am. Chem. Soc.*, **54**, 4172; 4183 (1932).
[15] STEWART and LI, *J. Am. Chem. Soc.*, **60**, 2782 (1938).

with reaction (XXI) rate determining in acetone solution and reaction (XX) determining at the relatively low acetone concentrations used in the alcohol solution. Reaction (XIX) is known to be mobile and reversible under the basic conditions of the experiments. The difficulty in accounting for the action of tertiary amines lies not in the fact that they catalyze but in the absence of catalysis by diethylamine, which would lead to a term in the square of the amine concentration in the rate equation.

Aldol-type Reactions: Basic Condensing Agents.—The aldol condensation is typical of a wide variety of synthetically important reactions that can be accounted for in terms of a mechanism of the following type:

$$H_3C - CHO + B \rightleftharpoons [H_2C - CHO]^- + BH^+ \tag{XXII}$$

$$[H_2C - CHO]^- + H_3C - CHO \rightleftharpoons \left[\begin{array}{c} H \\ | \\ H_3C - C - CH_2CHO \\ | \\ {}_{\cdot}O_{\cdot} \end{array} \right]^- . \tag{XXIII}$$

$$\left[\begin{array}{c} H \\ | \\ H_3C - C - CH_2CHO \\ | \\ {}_{\cdot}O_{\cdot} \end{array} \right]^- + BH^+ \rightleftharpoons H_3C - CHOH - CH_2 - CHO + B \tag{XXIV}$$
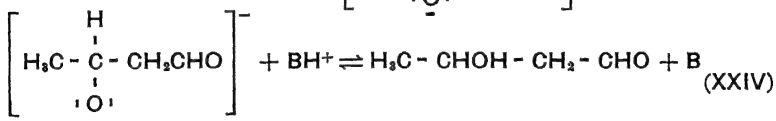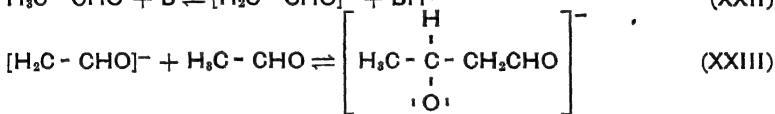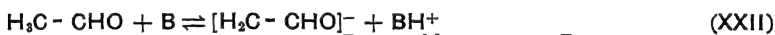
The reaction is the usual carbonyl addition, but the nucleophilic reagent which adds to the carbonyl carbon is derived from a second molecule of aldehyde by the loss of a proton from carbon. In the reaction of acetaldehyde the rate is first order in aldehyde and nearly proportional to the hydroxyl-ion concentration.[16] This indicates that reaction (XXII) is rate determining as does also the fact that no deuterium becomes attached to carbon when the reaction is run in deuterium water.[17] If the second step were rate determining, the first would be mobile and reversible and the pickup of deuterium on carbon would be faster than the condensation. There are minor quantitative deviations from the simple kinetics indicated: the rate at 25° satisfying the equation

$$v = [CH_3CHO]\{2.6 \times 10^{-4} + 0.111[OH^-]\} \tag{26}$$

in the range of sodium hydroxide concentrations from 0.003 to 0.03M but dropping off toward zero at lower concentrations.[16]

[16] BELL, *J. Chem. Soc.*, 1637 (1937).
[17] BONHOEFFER and WALTERS, *Z. physik. Chem.*, **A181**, 441 (1938).

That the first term of equation (21) does not represent a water catalysis is evidenced both by its disappearance at low alkali concentrations and by the failure of catalysis by other bases (carbonate and acetate ions) to appear. The complicating factor may be the hydration of the aldehyde.[16]

Aldolization is in general measurably reversible, although it goes nearly to completion with aldehydes. With acetone, on the other hand, the extent of polymerization to diacetone alcohol at equilibrium amounts to only a few per cent. The kinetics of the dealdolization have been extensively investigated.[18] The reaction is a strictly second-order one of diacetone alcohol with hydroxyl ion, and no catalysis by carboxylate ions has been observed, although there is a specific one by certain amines (page 362). · From the rate of dealdolization and the equilibrium constant the rate of aldolization of acetone can be calculated and is found to be about one-thousandth of the rate of iodination or of deuterium exchange under the same conditions.[19] In the system of reactions

$$CH_3COCH_3 + OH^- \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} [CH_3COCH_2]^- + H_2O \qquad (XXV)$$

$$[CH_3COCH_2]^- + CH_3COCH_3 \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} [CH_3COCH_2C(O)(CH_3)_2]^- \qquad (XXVI)$$

$$[CH_3COCH_2C(O)(CH_3)_2]^- + H_2O \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} CH_3COCH_2C(OH)(CH_3)_2 + OH^- \qquad (XXVII)$$
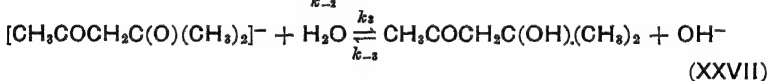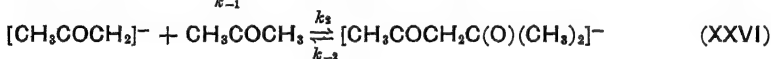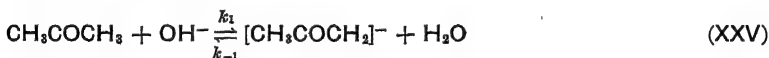
k_1, which determines the rate of halogenation or exchange, must therefore be much larger than the over-all rate of aldolization, which implies that reaction (XXVI) is rate determining. At the same time, the fact that the dealdolization rate is not measurably affected by the concentration of acetone[18b] demonstrates that reaction (XXVI) is rate determining in the reverse direction also.

The Amine Catalysis of Aldol Reactions.—The diacetone alcohol reaction is specifically catalyzed by ammonia and by primary and secondary amines. Tertiary amines catalyze only to an extent measured by the hydroxyl-ion concentration of their solutions, and the catalytic constants for other amines fail to

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[18] (a) KOELICHEN, *Z. physik. Chem.*, **33**, 129 (1900). (b) LA MER and MILLER, *J. Am. Chem. Soc.*, **57**, 2674 (1935).

[19] WALTERS and BONHOEFFER, *Z. physik. Chem.*, **A182**, 265 (1938).

satisfy the Brønsted law.[20] Some catalytic constants at 18.05°
are shown in Table IV, along with the basicity constants K_b of

TABLE IV.—CATALYTIC CONSTANTS IN THE DIACETONE ALCOHOL REACTION

Catalyst	OH⁻	CH_3NH_2	$(CH_3)_2NH$	$(CH_3)_3N$	$(C_2H_5)_3N$
10^4k	17.8	2.22	0.147	0	0
10^4K_b	....	3.2	3.4	0.32	3.2

the amines. A reasonable intermediate in terms of which to
account for this catalysis is the dipolar ion (I).[21] A substance of
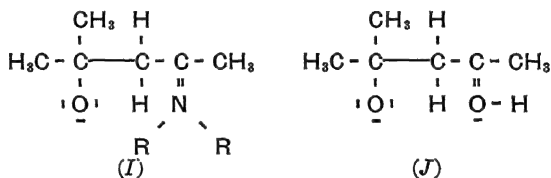
this type is possible with any amine except a tertiary one; because
of the greater basicity of nitrogen, it is more likely to be formed
than is the oxygen compound (J), and the accumulation of
negative charge on the left must favor the rupture into $(CH_3)_2CO$
and $CH_2\!=\!C(CH_3)NR_2$.

The Knövenagel, Perkin, and Related Reactions.—The conju-
gate base of the aldehyde that appears in reaction (XXIII) may
be replaced by a wide variety of carbanions. The general reac-
tion involves, therefore, a carbonyl compound, an acidic component,
and a base catalyst or condensing agent. As carbonyl
components, aldehydes are, as usual, more reactive then ketones.
As acidic component the most reactive substances are those of
relatively high acidity, like acetacetic ester, malonic ester,
cyanacetic ester, cyanacetamide, and aliphatic nitro compounds.
The reaction is also successful with simple ketones, esters, and the
like; with chloroform, acetylene, 2,4-dinitrotoluene, quinaldine,
and other α- and γ-alkyl pyridines and quinolines; and with

[20] MILLER and KILPATRICK, *J. Am. Chem. Soc.*, **53**, 3217 (1931. WEST-
HEIMER and COHEN, *ibid.* **60**, 90 (1938).

[21] WESTHEIMER, paper presented at the Conference on Kinetics of the
New York Academy of Sciences, April, 1939.

α,β-unsaturated aldehydes in which the γ-hydrogen is the acidic one. In most of these cases, independent evidence for the acidity of the proton involved is available from deuterium exchange or racemization (page 243).

In general it is to be expected that the minimum base strength required in the condensing agent should vary inversely with the inertia of the other reactants. Sodium carbonate, sodium acetate, or an amine is a sufficiently strong base in most cases, but it is probable that stronger bases, such as sodium ethylate, sodium amide, or sodium triphenylmethide will be required if a relatively weak acid or a sluggishly reacting carbonyl component is to be brought into reaction (*cf.* page 361).

The Perkin reaction involves the interaction of an aldehyde, an acid anhydride, and the sodium salt of the acid corresponding to the anhydride, and there has been considerable controversy as to whether the sodium salt or the anhydride reacts with the aldehyde. The same product, a mixture of C_6H_5CH=$CHCOOH$ and C_6H_5CH=$C(C_2H_5)COOH$ the composition of which varies with the temperature, is obtained from the reaction of benzaldehyde with butyric anhydride and sodium acetate and from that with acetic anhydride and sodium butyrate.[22] Evidently, an equilibrium is set up between the two anhydrides and the two salts, and such experiments yield no information on the problem in question. It is, however, quite improbable[22,23] that the loss of a proton from the negative ion of which the salt is composed should be as rapid or as extensive as it is from the electrically neutral anhydride. The conclusion that the anhydride reacts is strongly confirmed by the fact[24] that alkali carbonates, sulfites, and phosphates, or quinoline, pyridine, or triethylamine may be substituted for the alkali acetate. The function of the latter can, therefore, be no other than that of the B in equation (XXII).

There is little quantitative kinetic evidence on reactions of this type. The reaction of formaldehyde with malonic ester[25a] yields primarily $HOCH_2CH(CO_2C_2H_5)_2$, but this condenses fur-

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[22] BRESLOW and HAUSER, *J. Am. Chem. Soc.*, **61**, 786 (1939).

[23] ARNDT and EISTERT, *Ber.*, **69**, 2386 (1936).

[24] KALNIN, *Helv. Chim. Acta*, **11**, 977 (1928).

[25] (a) WELCH, *J. Chem. Soc.*, 653 (1931).   (b) ENKVIST, *J. prakt. Chem.* [II], **149**, 65 (1937).

ther at a comparable rate, and the kinetics are complicated. The initial rates of reaction in phosphate buffers of pH from 4.9 to 7.1 satisfy the equation

$$v = k[CH_2O][\text{ester}][OH^-] \tag{27}$$

Small amounts of ammonia or of triethylamine have no effect at a pH of 4.9 provided that enough acid is added to maintain an unchanged acidity, but piperidine in 0.001M concentration increases the rate sixfold under the same conditions. Methylamine produces a large acceleration, the transient nature of which may be due to the formation of unreactive $CH_3N\!\!=\!\!CH_2$. The failure of ammonia to accelerate the reaction may be due to an even more rapid formation of hexamethylentetramine.

Similar results are obtained in the reaction of formaldehyde with cyanacetamide.[25b] Ammonia, pyridine, and formate ion have no catalytic effect at constant pH; piperidine has a large one, the magnitude of which is greater, the higher the pH. This suggests that the base piperidine, not its conjugate acid, is the catalyst.

These results demonstrate the existence of a long suspected, but not previously proved, specific catalytic effect of secondary amines. The catalysis appears to be effective only in the presence of acids, since the addition of a small amount of piperidine to pure (*i.e.*, acid-free) aldehyde leads to no reaction unless a small amount of acid is also added.[26] Ordinary aldehydes contain enough acid impurity to permit the reaction. This effect must not be taken to require either that piperidinium ion be the actual catalyst or that the action of the piperidine and the acid be simultaneous (page 347).

Acid-catalyzed Aldol Condensations.—Aldolization is also catalyzed by acids. Since the conversion of an alcohol to an olefin is itself catalyzed by acids but not by bases, the acid-catalyzed aldol reaction frequently yields an unsaturated compound instead of an alcohol. Thus the action of bases on acetone yields diacetone alcohol, and that of acids leads to the corresponding olefin mesityl oxide, $(CH_3)_2C\!\!=\!\!CHCOCH_3$, and to the more highly condensed phorone. The acid- and the base-

[26] Kuhn, Badstübner, and Grundmann, *Ber.*, **69B**, 98 (1936).

catalyzed condensations may also involve different parts of the molecule; thus benzaldehyde condenses with methyl ethyl ketone to yield $C_6H_5CH=CHCOC_2H_5$ in alkaline solution but $C_6H_5CH=C(CH_3)COCH_3$ in acid.[27]   Citral, on the other hand, condenses with the methyl group in methyl ethyl ketone under either condition.[28]

An important condensation of this type is the one used in the malachite green synthesis in which the first step is no doubt

$$C_6H_5CHO + C_6H_5N(CH_3)_2 \rightarrow C_6H_5 - CHOH - C_6H_4N(CH_3)_2 \quad (XXVIII)$$
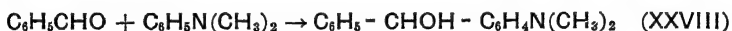
and is followed by the condensation of the very reactive benzhydrol derivative (page 309) with another molecule of amine.   The usual catalyst for this reaction is concentrated aqueous HCl, but the dimethylaniline must be present in amount more than equivalent to the acid, presumably because its conjugate acid is unreactive.

The mechanism of the acid-catalyzed condensation must involve the addition of a proton to the carbonyl component of the reaction, just as the base-catalyzed reaction involves the removal of a proton from the acidic component; one reaction depends upon a push where the other depends upon a pull.   The reaction of the strongly electrophilic ion (K) with dimethylaniline is of the

$$\left[\begin{array}{cc} \overset{\displaystyle H}{\underset{\displaystyle |}{\vphantom{|}}} & \overset{\displaystyle H}{\underset{\displaystyle |}{\vphantom{|}}} \\ C_6H_5 - C - \overset{..}{O} - H \longleftrightarrow C_6H_5 - C = \overset{..}{O} - H \end{array} \right]^+$$

$$(K)$$
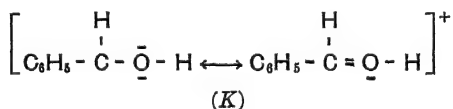
same type as the attack of electrophilic reagent on aromatic compound involved in the Friedel-Crafts reaction and in other reactions of aromatic compounds.   The reaction with acetone and the like probably is a similar reaction of (K) with the enolic form of acetone, the formation of which is rapid in acid media.

The Benzoin Condensation.—Formally, this is an aldol-type condensation in which the acidic hydrogen is the one attached to the carbonyl carbon

$$2C_6H_5CHO \rightarrow C_6H_5 - CHOH - CO - C_6H_5 \quad (XXIX)$$
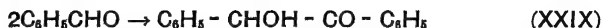
[27] HARRIES and MÜLLER, *Ber.*, **35**, 966 (1902).
[28] PAPA, Thesis, Columbia, 1937.

Cyanide ion is a powerful specific catalyst, apparently an indispensable one; consequently, the analogy to the aldol reaction is superficial. The rate law is[29]

$$v = k[C_6H_5CHO]^2[CN^-] \qquad (28)$$

The value of k in 60 per cent by volume ethanol at 60° is 0.0015 and increases moderately with increasing water content (40 per cent in the range from 83 to 39 per cent ethanol). Neither sodium hydroxide nor the weakly ionized hydrocyanic acid and mercuric cyanide have any appreciable effect on the rate, and the specific rate has the same value in sodium, potassium, and barium cyanide solutions. The mechanism is no doubt[30]

$$(XXX)$$

$$(XXXI)$$

$$(XXXII)$$

$$(XXXIII)$$
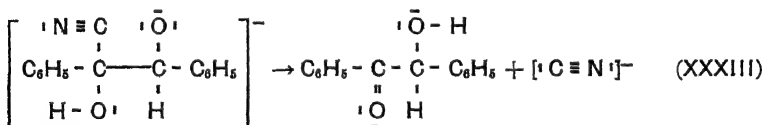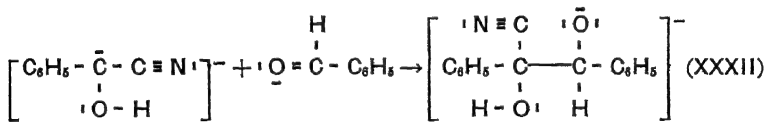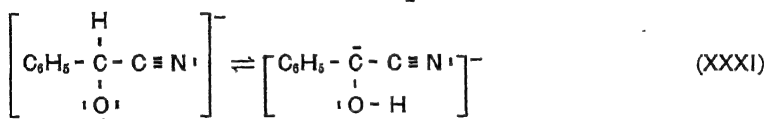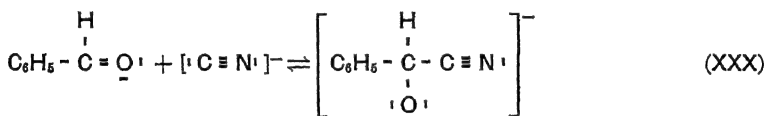
Reaction (XXX) is mobile and reversible under the conditions prevailing, and the function of the cyanide is clearly to facilitate the protropic reaction (XXXI) by virtue of the loosening effect that a cyanide group has upon α-hydrogen (as in cyanacetic ester and cyanacetamide). The kinetics require that reaction (XXXII) or (XXXIII) be rate determining, that acetone cyanhydrine be at least as strong an acid as HCN, and that the

[29] BREDIG and STERN, *Z. Elektrochem.*, **10**, 582 (1904).
[30] LAPWORTH, *J. Chem. Soc.*, **83**, 995 (1903).

concentrations of all the intermediates be small.   The first condition is implied by the second-order dependence on aldehyde concentration, and the second by the absence of any acceleration by sodium hydroxide.   The cyanhydrine must be so completely converted to its conjugate base by cyanide ion that an increase in alkalinity does not appreciably increase the extent of the reaction.   The third condition is reasonable in spite of the fact that the proportion of cyanhydrine in equilibrium with acetone and HCN is large at room temperatures; for the equilibrium constant for cyanhydrine formation decreases rapidly with increasing temperature.

An electron-repelling substituent such as $(CH_3)_2N$ must decrease the acidity of the aldehyde or cyanhydrine hydrogen, increase the nucleophilic reactivity of the ion, and decrease the electrophilic reactivity of the aldehyde molecule which acts as carbonyl component in reaction (XXXII).   In benzaldehyde itself, the balance of these effects is favorable; it is not so favorable either in p-methoxy or p-chlor benzaldehyde, and p-dimethylaminobenzaldehyde yields no benzoin.   But a mixture of benzaldehyde and its dimethylamino derivative reacts readily to yield the mixed benzoin C_6H_5—CO—CHOH—$C_6H_4N(CH_3)_2$.[31]

The Cannizaro and Related Reactions.—The Cannizaro reaction of furfural

$$2RCHO + OH^- \rightarrow RCH_2OH + RCOO^- \qquad \text{(XXXIV)}$$
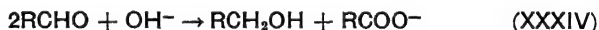
in homogeneous aqueous or aqueous-alcoholic solution is of the fourth order[32]

$$v = k[RCHO]^2[OH^-]^2 \qquad (29)$$

In spite of careful search no signs of retardation by antioxidants or of acceleration by oxidizing agents have been detected.   The Cannizaro reaction of benzaldehyde[33a] in aqueous-alcoholic solution may also be interpreted, although with less certainty, as

[31] STAUDINGER, *Ber.*, **46**, 3535 (1913).

[32] GEIB, *Z. physik. Chem.*, **A169**, 41 (1934).

[33] (*a*) POMERANZ, *Monats.*, **21**, 389 (1900).   (*b*) EULER and LÖVGREN, *Z. anorg. allgem. Chem.*, **147**, 123 (1925).

indicating a fourth-order reaction, as may that of formaldehyde,[33b] provided that the pronounced acidity of that substance is taken into account. The reaction of benzaldehyde, formaldehyde, or glyoxal in deuterium water does not result in an alcohol containing deuterium attached to carbon;[34] consequently, the process involves the transfer of a hydrogen atom from one aldehyde molecule to another without interchange with the solvent. These phenomena are consistent with the following mechanism:

$$R-C\overset{H}{\underset{O}{\diagup}} + 2OH^- \rightleftharpoons \left[R-\overset{H}{\underset{O}{\overset{|}{C}}}-\bar{O}\right]^- + H_2O \qquad (XXXV)$$

$$\left[R-\overset{H}{\underset{O}{\overset{|}{C}}}-\bar{O}\right]^- + O=\overset{R}{\underset{H}{C}} \rightarrow \left[R-C=\bar{O}\right]^- + \left[\bar{O}-\overset{H}{\underset{H}{\overset{|}{C}}}-R\right]^- \qquad (XXXVI)$$

$$\left[R-\overset{H}{\underset{H}{\overset{|}{C}}}-\bar{O}\right]^- + H_2O \rightarrow R-\overset{H}{\underset{H}{\overset{|}{C}}}-\bar{O}-H + OH^- \qquad (XXXVII)$$
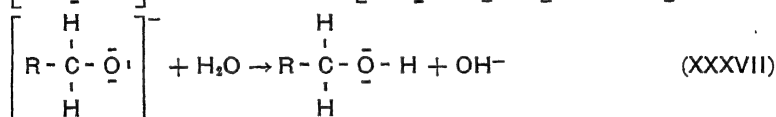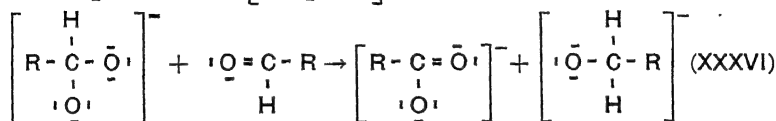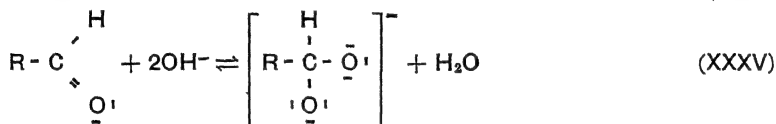
The high concentration of negative charge in the ion produced by reaction (XXXV) is responsible for the transfer of a hydride ion to another aldehyde molecule in reaction (XXXVI).

The internal Cannizaro reaction of glyoxal involves the typical one-atom shift of a hydride ion, which appears in so many rearrangements; in fact, it is a benzilic acid rearrangement with hydrogen instead of phenyl shifting

$$\left[O=\overset{H}{\underset{O-H}{\overset{|}{C}}}-\overset{H}{\underset{|}{C}}-\bar{O}\right]^- \rightarrow \left[\bar{O}-\overset{H}{\underset{H}{\overset{|}{C}}}-C\overset{\bar{O}}{\underset{O-H}{\diagup}}\right]^- \rightarrow \left[H-\bar{O}-\overset{H}{\underset{H}{\overset{|}{C}}}-\overset{\bar{O}}{\overset{||}{C}}-\bar{O}\right]^-$$

(XXXVIII)
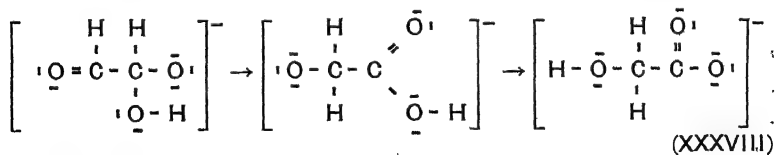
The rate of the Cannizaro reaction is increased by electron-attracting substituents, the relative values in aqueous solution

[34] FREDENHAGEN and BONHOEFFER, *Z. physik. Chem.*, **A181**, 379 (1938).

being as follows:[35] p-methoxybenzaldehyde, 0.140; p-methyl-benzaldehyde, 0.065; benzaldehyde, 1; p-chlorbenzaldehyde, 9.4.

Under anhydrous conditions, as when benzaldehyde is treated with sodium benzylate, the reaction product is an ester. A probable mechanism is

$$
R-C{\overset{\bar{O}}{\underset{H}{}}} + \left[\overset{H}{\underset{H}{\bar{O}-C-R}} \right]^- \rightarrow \left[R-\overset{\bar{O}}{\underset{H}{C}}-\bar{O}-\overset{H}{\underset{H}{C}}-R \right]^- \tag{XXXIX}
$$

$$
\left[R-\overset{\bar{O}}{\underset{H}{C}}-\bar{O}-\overset{H}{\underset{H}{C}}-R \right]^- + \overset{H}{\bar{O}=C-R} \rightarrow R-\overset{\bar{O}}{\underset{H}{C}}-\bar{O}-\overset{H}{\underset{H}{C}}-R + \left[\overset{H}{\underset{H}{\bar{O}-C-R}} \right]^- \tag{XL}
$$
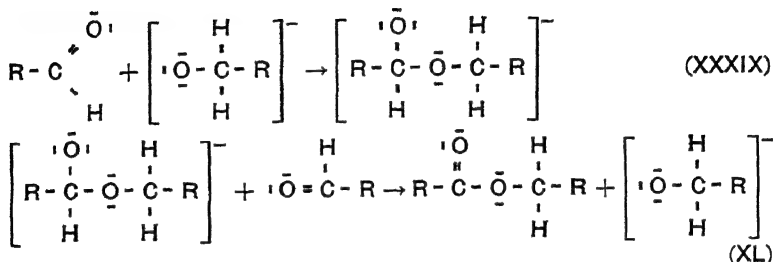
Benzyl benzoate is so resistant to hydrolysis that it is improbable that the reaction in aqueous solution follows this or any other course that involves the formation and hydrolysis of this ester.

The same conversion of aldehyde to ester may be produced by the electrophilic reagent aluminum alcoholate.[36] In this case the effect of the catalyst must be upon the reactant molecule that receives the hydride ion, just as it is on the donor molecule in the case of basic catalysts, the active intermediate being (L)

$$
R-C{\overset{H}{\underset{\underset{(L)}{\bar{O}-Al(OR')_2}}{}}}
$$
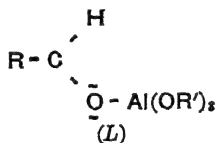
The electrophilic aluminum atom makes the carbonyl carbon so positive that it can abstract a hydride ion from another aldehyde molecule or even from an alcohol molecule as in the reduction of aldehyde by i-propyl alcohol[37]

[35] MOLT, Rec. trav. chim., 56, 233 (1937).

[36] TISCHTSCHENKO, Chem. Zentr., 77, II, 1309; 1552 (1906).

[37] The literature of this important reaction, which was discovered nearly simultaneously by several investigators, is reviewed by Lund, Ber., 70, 1520 (1937).

$$R - C \overset{H}{\underset{\bar{O} - Al(OR')_3}{\diagdown}} + H - \bar{O} - \overset{H}{\underset{CH_3}{\overset{|}{C}}} - CH_3 \rightleftharpoons \left[R - \overset{H}{\underset{H}{\overset{|}{C}}} - O - Al(OR')_3 \right]^{--} +$$

$$\left[H - \bar{O} - C \overset{\diagup CH_3}{\underset{\diagdown CH_3}{}} \right]^{+} \quad (XLI)$$
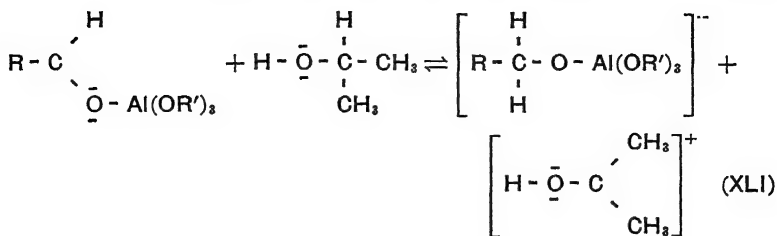
Electrophilic reagents like $ZnCl_2$, $AlCl_3$, and $HgCl_2$ are active promoters for the action of aluminum ethylate on aldehydes.[38]

The Hydrolysis of Hydrocyanic Acid and of Nitriles.—The hydrolysis of hydrocyanic acid[39] by hydrochloric acid is rigidly first order in HCN over the range from 0.8 to 2.5M concentration. The specific rate varies approximately as the activity of molecular HCl or as the product of the activities of oxonium and chloride ions. This leads to a rapid change in rate, which at 65° increases from 8.1×10^{-5} in 0.302M HCl to 3.50×10^{-4} in 5.52M acid. At low concentrations all strong acids are about equally effective catalysts; at high concentrations they differ widely, HBr giving a rate one-tenth that of HCl, and H_2SO_4, with a specific rate of 5.4×10^{-6} at 5.49M concentration, being a very poor catalyst. The reaction at high acidities evidently depends upon the reaction of the anion of the acid as well as of a proton, presumably by way of $HC(Cl)=NH$ or a similar intermediate. At lower acidities a reaction with oxonium ion predominates, for the catalytic effects of the different acids are the same. Formamide is a probable intermediate; as its own specific rate of hydrolysis in 2M HCl is 14,000 times faster than that of hydrocyanic acid, it cannot be detected.

The hydrolysis of a variety of nitriles[40] shows a similar dependence upon the nature and concentration of the catalyzing acid. Amides are not isolable for the same reason as in the case of hydrocyanic acid. Specific rates times 10^7 at 65° in 4M HCl are as follows: HCN, 710; CH_3CN, 5.8; C_2H_5CN, 10.0; $HOOCCH_2$-CN, 3.3; $CH_3CHOHCN$, 78; CH_2OHCH_2CN, 5.3. The relative

[38] CHILD and ADKINS, *J. Am. Chem. Soc.*, **45**, 3013 (1923).

[39] KRIEBLE and McNALLY, *J. Am. Chem. Soc.*, **51**, 3368 (1929). KRIEBLE and PEIKER, *ibid.*, **55**, 2326 (1933).

[40] KRIEBLE and NOLL, *J. Am. Chem. Soc.*, **61**, 560 (1939).

ineffectiveness of sulfuric acid in these reactions can be utilized for preparative purposes. Thus strong aqueous hydrochloric acid acts on amygdalin chiefly to hydrolyze the nitrile group, whereas sulfuric acid yields glucose and mandelonitrile.

The Aldchlorimine Reaction.[41]—The reaction is a second-order

$$R - CH = N - Cl + B \rightarrow R - C \equiv N + BH^+ + Cl^- \qquad (XLII)$$

one between imine and base. For a series of amines the rate parallels the base strength of the amine. When R is a substituted phenyl, the usual linear free-energy relationship applies (page 190) with meta and para derivatives, and ortho derivatives show a specific retardation. The probable mechanism[41b] is

$$R - CH = \bar{N} - \bar{C}l \cdot + B \rightleftharpoons [R - \bar{C} = \bar{N} - \bar{C}l \cdot]^- + BH^+ \qquad (XLIII)$$

$$[R - \bar{C} = \bar{N} - \bar{C}l \cdot]^- \rightarrow R - C \equiv N \cdot + Cl^- \qquad (XLIV)$$
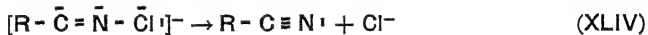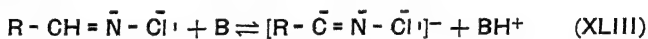
It is not known whether the catalysis is of the general base or of the specific hydroxyl-ion type.

Ester Reactions: Alkaline Hydrolysis.—The alkaline hydrolysis of an ester is a second-order reaction between ester and hydroxyl ion. With carboxylic esters the rupture of the ester molecule occurs on the acid rather than on the alcohol side of the ether linkage. This is conclusively demonstrated in the case of amyl acetate by experiments on the hydrolysis in water containing more than the normal proportion of the oxygen isotope of mass 18, whereas the ester contains oxygen of normal isotopic composition.[42] By thus "labeling" the oxygen of the ester and of the water, it is possible to prove that the oxygen in the amyl alcohol formed by the hydrolysis comes from the ester, not from the water.

The generality of this conclusion is indicated by a variety of evidence. The esterification, followed by the alkaline hydrolysis, of a carboxylic ester has never led to an inversion of configuration of the carbinol carbon,[43] as it should if the linkage of oxygen to

[41] (a) HAUSER and MOORE, *J. Am. Chem. Soc.*, **55**, 4526 (1933).   (b) HAUSER, LeMAISTRE, and RAINSFORD, *ibid.*, **57**, 1056 (1935).

[42] POLANYI and SZABO, *Trans. Faraday Soc.*, **30**, 508 (1934).

[43] HOLMBERG, *Ber.*, **45**, 2997 (1912). FISCHER, *Ann.*, **394**, 360 (1912). HÜCKEL and FRANK, *ibid.*, **477**, 137 (1930). VERKADE, *ibid.*, **477**, 287; 297 (1930).

this carbon were involved, and as it does in the case of the sulfonic esters (page 160). Esters of α,β-unsaturated alcohols do not rearrange under conditions of alkaline hydrolysis,[44] as would be expected were the hydrolysis a reaction of the carbonium-ion type. Finally,[45] the effect of the structure of the acyl group on the rate of hydrolysis closely parallels that in the reaction

$$RCOOCH_3 + NH_3 \rightarrow RCONH_2 + CH_3OH \qquad (XLV)$$

but shows no relation to that in the reaction

$$RCOOCH_3 + N(CH_3)_3 \rightarrow RCOO^- + N(CH_3)_4^+ \qquad (XLVI)$$

Esters of sulfuric acid and of the sulfonic acids, on the other hand, react by way of a rupture of the alkyl-oxygen linkage.[46] These are effective alkylating agents, *i.e.*, they alkylate ammonia or amines by a reaction analogous to (XLVI), whereas carboxylic esters acylate them by reaction (XLV), and their hydrolysis inverts the configuration of the alkyl group (page 160). Even with carboxylic esters the reaction in alkaline solution may be a water reaction rather than one with hydroxyl ion, and the water reaction in some cases at least ruptures the alkyl-oxygen linkage and inverts the configuration of the alcohol (page 177).

A satisfactory mechanism for the hydrolysis of carboxylic esters involves the addition of hydroxyl ion to the carbonyl carbon, followed or accompanied by the release of the alkyloxy group
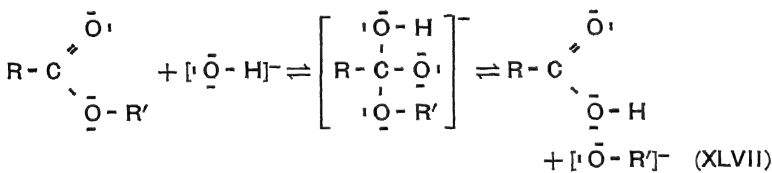
The attachment of the hydroxyl ion must, of course, weaken the linkage of the alkyloxy ion.

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[44] INGOLD and INGOLD, *J. Chem. Soc.*, 756 (1932).

[45] (a) HAMMETT and PFLUGER, *J. Am. Chem. Soc.*, **55**, 4079 (1933). (b) BETTS and HAMMETT, *ibid.*, **59**, 1568 (1937).

[46] FERNS and LAPWORTH, *J. Chem. Soc.*, **101**, 273 (1912).

There is evidence for a catalysis of the hydrolysis by acetate ion.[47] This cannot, however, be a truly general base catalysis since the rate of hydrolysis in ammonia-ammonium ion buffers is determined by the hydroxyl-ion concentration of the solution.[48] If acetate ion plays the part of the hydroxyl ion in reaction (XLVII), the acid anhydride formed would probably be rapidly hydrolyzed.

The alkaline hydrolysis is effectively irreversible, not because the linkage of carbon to hydroxyl ion is firmer than that to alkyloxy ion, but because the RCOOH produced in reaction (XLVII) is immediately converted by the alkali to $RCOO^-$. This is not true in the otherwise analogous conversion of the ester of one alcohol to that of another, *e.g.*,

$$CH_3COOC_6H_5 + C_2H_5O^- \rightleftharpoons CH_3COOC_2H_5 + C_6H_5O^- \quad \text{(XLVIII)}$$

These *Umesterung* reactions may generally be driven well toward completion in either direction by the action of an excess of the one or the other alcohol. They are catalyzed by acids and by bases, and their rates show a dependence on the structure of the acyl group similar to that of the hydrolysis.[49]

Acid-catalyzed Esterification and Hydrolysis.—The acid-catalyzed reaction is reversible and may be made effectively complete in either direction by excess of water or of alcohol. The equilibrium constant is nearly the same for all esters (page 213). Like the alkaline hydrolysis the esterification leaves the alkyl-oxygen linkage untouched. Thus[50] the reaction of benzoic acid containing oxygen of normal isotopic composition with methyl alcohol containing a larger proportion of O^{18} goes as follows:

$$C_6H_5C \overset{O^{16}}{\underset{O^{16}-H}{\diamond}} + CH_3-O^{18}-H \rightarrow C_6H_5C \overset{O^{16}}{\underset{O^{18}-CH_3}{\diamond}} + H_2O^{16} \quad \text{(XLIX)}$$
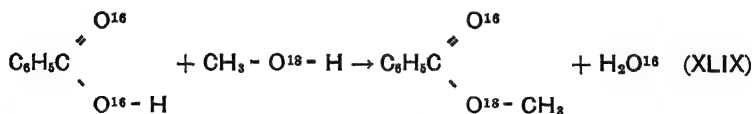
[47] DAWSON and LOWSON, *J. Chem. Soc.*, 2444 (1927).

[48] ARRHENIUS, *Z. physik. Chem.*, **2**, 289 (1888).

[49] JONES and LAPWORTH, *Proc. Chem. Soc.*, **30**, 141 (1914). TOWNSHEND, *C. A.*, **24**, 2119 (1930).

[50] ROBERTS and UREY, *J. Am. Chem. Soc.*, **60**, 2391 (1938); **61**, 2584 (1939).

The catalysis has been shown to be of the general acid type in the esterification of acetic acid.[47,51] The so-called uncatalyzed esterification of acetic acid, *viz.*, the esterification in the absence of a deliberately added catalyst, is consequently a complicated process in which the acetic acid as well as the lyonium ion produced by its reaction with the solvent accelerates the reaction. The rate in methyl alcohol is given by[51c]

$$v = \{k_0[\text{HAc}][\text{CH}_3\text{OH}_2{}^+] + k_1[\text{HAc}]^2 + k_2\} \tag{30}$$

The first term represents catalysis by the lyonium ion, the second catalysis by molecular acetic acid, and the third catalysis by some substance, perhaps the lyate ion CH_3O^-, the concentration of which varies inversely with that of acetic acid.

The mechanism of the acid-catalyzed esterification and hydrolysis[50,52] probably involves the addition of alcohol or of water to the carbonyl double bond with the monoester of the ortho acid as an intermediate

$$
R-C\overset{\bar{O}}{\underset{\bar{O}-H}{}} + HA \rightleftharpoons \left[R-C\overset{\bar{O}-H}{\underset{\bar{O}-H}{}}\right]^+ + A^- \tag{L}
$$

$$
\left[R-C\overset{\bar{O}-H}{\underset{\bar{O}-H}{}}\right]^+ + ROH \rightleftharpoons \left[R-\overset{\bar{O}-H\ \ R}{\underset{\bar{O}-H\ \ H}{\underset{|}{\overset{|}{C}}-\bar{O}}}\right]^+ \tag{LI}
$$

$$
\left[R-\overset{\bar{O}-H\ \ R}{\underset{\bar{O}-H\ \ H}{\underset{|}{\overset{|}{C}}-\bar{O}}}\right]^+ + A^- \rightleftharpoons R-\overset{\bar{O}-H}{\underset{\bar{O}-H}{\underset{|}{\overset{|}{C}}-\bar{O}}}-R + HA \tag{LII}
$$
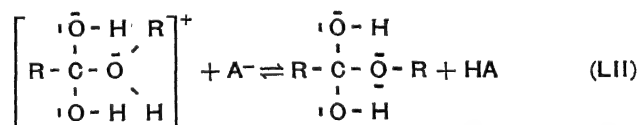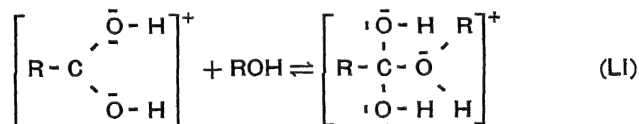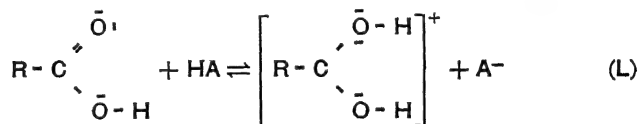
The ester is then formed by a series of reactions analogous to the reversal of this process but with HOH instead of ROH splitting off. The process is closely related to the semicarbazone reaction (page 333) and resembles it in showing general acid

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[51] (a) GOLDSCHMIDT, *Ber.*, **29**, 2208 (1896); *Z. Elektrochem.*, **15**, 4 (1909). (b) DAWSON, PYCOCK, and SPIVEY, *J. Chem. Soc.*, 291 (1933). (c) ROLFE and HINSHELWOOD, *Trans. Faraday Soc.*, **30**, 935 (1934).

[52] DATTA, DAY, and INGOLD, *J. Chem. Soc.*, 838 (1939). HUGHES, INGOLD, and MASTERMAN, *ibid.*, 840 (1939).

catalysis and a pronounced retardation by ortho or alpha substituents. The pronounced steric hindrance excludes the mechanism

$$R - C \overset{\bar{O}\,'}{\underset{\bar{O} - H}{\diagdown}} + HA \rightleftharpoons [R - C = \bar{O}\,']^+ + H_2O + A^- \qquad (LIII)$$

$$[R - C = \bar{O}\,']^+ + ROH + A^- \rightleftharpoons R - C \overset{\bar{O}\,'}{\underset{\bar{O} - R}{\diagdown}} + HA \qquad (LIV)$$
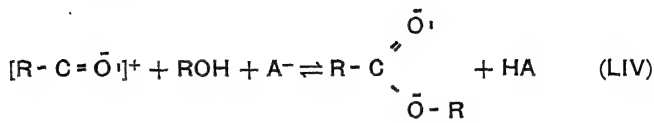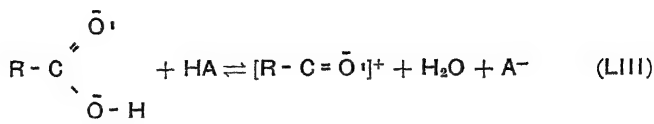
because this kind of reaction is facilitated rather than hindered by ortho methyl groups.[53] Reaction (LIII) does occur in concentrated sulfuric acid with 2,4,6-trimethylbenzoic acid but not with benzoic (page 55), and the same acyl ion is rapidly formed from the methyl ester of the trimethyl benzoic acid in sulfuric acid, although methyl benzoate is only slowly acted on by the same reagent.

As in the enolization of acetophenone, and probably for the same reason, the rate of the acid-catalyzed esterification and hydrolysis does not parallel the base strength of acid or ester. Thus phenylacetic acid is a slightly weaker base than benzoic acid;[54] its rate of esterification is some 200 times greater. Consequently, reaction (L) cannot be rate determining.

The Water Reaction in Ester Hydrolysis.—With most carboxylic esters the reaction with water is of subordinate importance compared with the reaction with hydroxyl ion and with oxonium ion. In the case of the stronger acids, carboxylic or not, the water reaction is, however, of considerable importance, and the acid-catalyzed reaction becomes negligible.[55] This is true of trichloracetic, oxalic, picric, nitric, phosphoric, sulfuric, and arylsulfuric esters. The hydrolysis of lactones also shows

[53] TREFFERS and HAMMETT, *J. Am. Chem. Soc.*, **59**, 1708 (1937).

[54] FLEXSER, HAMMETT, and DINGWALL, *J. Am. Chem. Soc.*, **57**, 2103 (1935).

[55] WEGSCHEIDER, *Z. physik. Chem.*, **41**, 52 (1902). PRÄTORIUS, *Monatsh.*, **26**, 1 (1905). OLIVIER and BERGER, *Rec. trav. chim.*, **41**, 637 (1922); **46**, 861 (1927). DEMÉNY, *ibid.*, **50**, 60 (1931). CAVALIER, *Ann. chim.* [7], **18**, 449 (1899).

a relatively large water reaction, which appears to invert the configuration of the carbinol carbon and to involve an alkyl-oxygen rupture rather than the acyl-oxygen rupture of the acid and alkaline hydrolysis (page 177). A similar situation is indicated[56] by the fact that the acid phthalate ester of the alcohol C_6H_5—CH=CH—CHOH—CH_3 is hydrolyzed without racemization by sodium hydroxide but is extensively racemized when weak bases like sodium carbonate are used.

The Reaction of Esters with Ammonia.—The reaction of methyl phenylacetate with ammonia in methanol solution[455]

$$R-C{\overset{O}{\underset{OCH_3}{}}} + NH_3 \rightarrow R-C{\overset{O}{\underset{NH_2}{}}} + CH_3OH \qquad (LV)$$
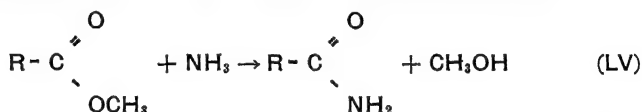
is retarded by ammonium salts and accelerated by sodium methylate. There are apparently two competing reactions, one of ester with ammonia, the other of ester with amide ion. The kinetics satisfy the equations

$$v = k_1[RCO_2CH_3][NH_3] + k_2[RCO_2CH_3][NH_2^-] \qquad (31)$$
$$v = k_1[RCO_2CH_3][NH_3] + k_2[RCO_2CH_3][NH_3][CH_3O^-] \qquad (32)$$

The effect of substituents in the phenyl group is correlated by a linear free-energy relationship with that in the alkaline hydrolysis of the same esters. The effect of the structure of the alkyl group on the amide reaction is also similar to that in the hydrolysis,[57] the rates of amide formation from normal, secondary, and tertiary butyl acetates in 40 per cent ethanol being as 24:6:1.

In liquid ammonia the reaction of ethyl benzoate and of other esters is accelerated by ammonium salts, the effect of different ammonium salts being relatively the same as in other reactions in this solvent.[58] In this medium there is, therefore, an acid catalysis (by ammonium ion) in contrast to the base catalysis in methanol.

Reactions of Esters with Carbanions: Grignard Addition: Claisen Condensation.—The reaction of the Grignard reagent

[56] KENYON, PARTRIDGE, and PHILLIPS, *J. Chem. Soc.*, 85 (1936).

[57] FRENCH, JOHNSON, and RATEKIN, *J. Am. Chem. Soc.*, **58**, 1346 (1936).

[58] FELLINGER and AUDRIETH, *J. Am. Chem. Soc.*, **60**, 579 (1938). AUDRIETH and KLEINBERG, *J. Org. Chem.*, **3**, 312 (1938).

with an ester involves the addition of the carbanion of the reagent to the ester carbonyl

$$R - C \overset{\bar{O}}{\underset{\bar{O} - R'}{\diagdown}} + R'' - Mg^+ \rightarrow \left[R - \overset{R''}{\underset{\bar{O} - R'}{C}} - \bar{O} \right]^- + Mg^{++} \qquad (LVI)$$
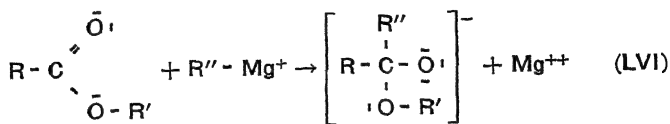
Loss of the ion OR'^- forms the ketone $R'COR''$, which may then react further to form the conjugate base of the tertiary alcohol $R'R_2''COH$. In agreement with the close similarity in mechanism the effect of the structure of the ester in this reaction closely parallels that observed in the alkaline ester hydrolysis (page 212).

In the Claisen condensation, ethyl acetate is converted to ethyl acetoacetate by sodium alcoholate (or by the action of sodium on ester containing traces of alcohol). It obviously depends on the addition of the carbanion formed by the action of the base on one molecule of the ester to the carbonyl group of another ester molecule and is, therefore, closely related to aldol condensation and Perkin synthesis

$$CH_3C \overset{O}{\underset{OC_2H_5}{\diagdown}} + OC_2H_5^- \rightleftharpoons \left[CH_2C \overset{O}{\underset{OC_2H_5}{\diagdown}} \right]^- + C_2H_5OH \qquad (LVII)$$

$$CH_3C \overset{\bar{O}}{\underset{\bar{O} - C_2H_5}{\diagdown}} + \left[CH_2C \overset{\bar{O}}{\underset{OC_2H_5}{\diagdown}} \right]^- \rightarrow \left[CH_3 - \overset{\bar{O}}{\underset{\bar{O} - C_2H_5}{C}} - CH_2 - C \overset{\bar{O}}{\underset{\bar{O} - C_2H_5}{\diagdown}} \right]^- \qquad (LVIII)$$

$$\rightarrow CH_3 - \overset{\bar{O}}{\overset{\|}{C}} - CH_2 - C \overset{\bar{O}}{\underset{\bar{O} - C_2H_5}{\diagdown}} + C_2H_5O^- \qquad (LIX)$$
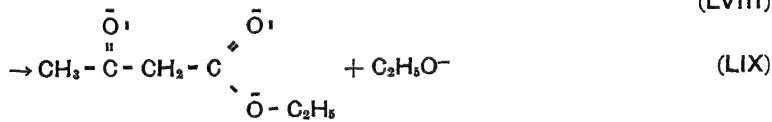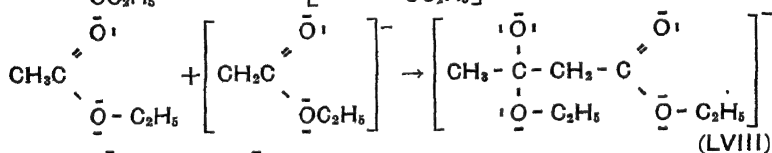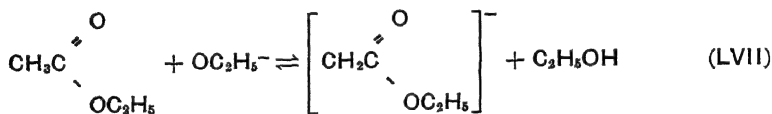
The value of this mechanism is demonstrated by its success in predicting the means necessary to make the reaction occur with ethyl isobutyrate, which does not condense under the action of sodium alcoholate.[59] Reactions of the type of (LVII) are

[59] HAUSER and RENFROW, *J. Am. Chem. Soc.*, **59**, 1823 (1937). RENFROW and HAUSER, *ibid.*, **60**, 463 (1938).

strongly retarded by substitution of alkyl for hydrogen on the carbon that carries the acidic proton, but the resultant sluggishness of the isobutyrate may be counteracted by the use of a stronger base. With sodium triphenylmethide the condensation goes easily and rapidly and the yield is 36 per cent. With the same condensing agent a mixture of ethyl isobutyrate and ethyl benzoate yields ethyl benzoyldimethylacetate if the reaction mixture is worked up within half an hour, but ethyl isobutyrylisobutyrate if it is allowed to stand for several days. This is another example of the fact that the most rapidly formed product is not necessarily the most stable one; further it demonstrates the reversibility of the condensation.

Another powerful base that induces the condensation of ethyl isobutyrate is 2,4,6-trimethylphenyl magnesium bromide.[60] Like all Grignard reagents this is a very strong base; unlike most, it does not add to the ester carbonyl by equation (LVI), and it may, therefore, act as a base.

Direct evidence of the reversibility of the Claisen condensation is easily obtained in alcoholic solution at 60° with either acids or sodium ethylate as catalyst.[61]

Decomposition of Acetacetic Ester and Related Substances.— The "acid decomposition" favored by strong aqueous alkali amounts to the reversal of the Claisen condensation stabilized by the conversion of ester to unreactive acetate ion.

The "ketonic decomposition" is probably preceded by the hydrolysis of the ester, and the decomposition of acetacetic acid and its derivatives and related substances has been investigated in detail. The kinetics of the decomposition of acetacetic acid itself[62] indicate the presence of two parallel reactions, one of molecular acetacetic acid, the other of acetoacetate ion, with the first fifty times faster than the second.

α,α-Dimethylacetacetic acid[63] decomposes 4.2 times faster than the unsubstituted acid, the specific rate at 24.97° being 6.96×10^{-5}. Dimethylacetoacetate ion decomposes at the same temperature with a specific rate of 1.5×10^{-8}. The rate in

[60] SPIELMAN and SCHMIDT, *J. Am. Chem. Soc.*, **59**, 2009 (1937).

[61] BECKMANN and ADKINS, *J. Am. Chem. Soc.*, **56**, 1119 (1934).

[62] WIDMARK, *C. A.*, **15**, 2763 (1921).

[63] PEDERSEN, *J. Am. Chem. Soc.*, **51**, 2098 (1929); *ibid.*, **58**, 240 (1936).

glycollate buffers is quantitatively that predicted from these figures and the known ionization constant of dimethylacetacetic acid; hence, there is no general acid or base catalysis. The reaction is exclusively of the ketonic type and yields methyl-i-propyl ketone and carbon dioxide. When the reaction is run in the presence of bromine or iodine, its rate is unchanged, but the sole product is a brominated ketone although methyl-i-propyl ketone is not brominated under the prevailing conditions. These phenomena are consistent with the assumption[66] that the actual reactant is a dipolar ion the concentration of which is proportional to that of the molecular acid

$$CH_3 - \overset{\overset{\displaystyle \bar{O} \cdot}{\|}}{C} - C(CH_3)_2 - C \overset{\displaystyle \bar{O} \cdot}{\underset{\displaystyle \bar{O} - H}{\diagdown}} \rightleftharpoons CH_3 - \overset{\overset{\displaystyle \cdot \bar{O} - H}{\cdot}}{C} - C(CH_3)_2 - \overset{\overset{\displaystyle \bar{O} \cdot}{\|}}{C} - \bar{O} \cdot \rightarrow$$

$$CH_3 - \overset{\overset{\displaystyle \cdot \bar{O} - H}{\cdot}}{C} = C(CH_3)_2 + CO_2 \quad (LX)$$
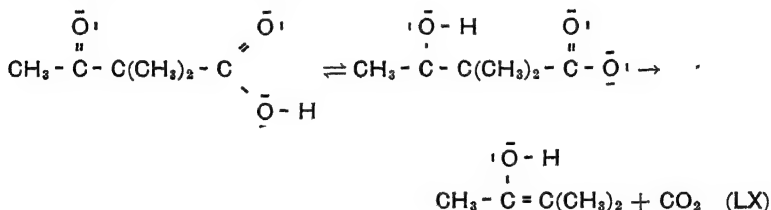
In the presence of halogen the enol, which is the immediate reaction product, is instantaneously halogenated. The decomposition of the acetoacetate ion presumably leads to the conjugate base of the ketone

$$\left[CH_3 - \overset{\overset{\displaystyle \bar{O} \cdot}{\|}}{C} - C(CH_3)_2 - \overset{\overset{\displaystyle \bar{O} \cdot}{\|}}{C} - \bar{O} \cdot \right]^- \rightarrow \left[CH_3 - \overset{\overset{\displaystyle \bar{O} \cdot}{\|}}{C} = C(CH_3)_2 \right]^- + CO_2 \quad (LXI)$$
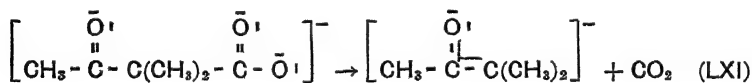
These decompositions show a pronounced catalysis by primary amines[64] which is not a general base catalysis since other amines are ineffective. The reaction of the dimethylacetacetic acid in aniline or o-chloraniline buffers satisfies the following equation:

$$v = k_0[HA] + k_1[A^-] + k_2[B][HA] + k_3[B]^2[HA] + k_4[BH^+][HA] \tag{33}$$

in which HA is the acetacetic acid, A^- its anion, and B the amine. At $24.97°$ the constants are as follows:

[64] WIDMARK and JEPPSSON, *C. A.*, **16**, 1962 (1922). PEDERSEN, *J. Am. Chem. Soc.*, **60**, 595 (1938).

Catalyst	k_0	k_1	k_2	k_3	k_4
Aniline........	6.96×10^{-5}	1.5×10^{-8}	0.0184	0.0164	0
o-Chloraniline..	6.96×10^{-5}	1.5×10^{-8}	0.00124	0	1.21×10^{-4}

The term involving k_2 has been attributed[66] to the reaction of a dipolar ion of the structure (M)

$$CH_3 - C \Big\langle \begin{array}{c} C(CH_3)_2 - \overset{\overset{\bar{O}}{\underset{\parallel}{}}}{C} - \bar{O} \\ \\ N - C_6H_5 \\ | \\ H \end{array} \\ (M)$$
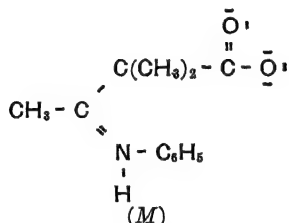
Because of the greater basicity of nitrogen, the concentration of this substance may well be larger than that of the dipolar ion intermediate in reaction (LX).

Dibrommalonic acid decomposes at a rate proportional to the concentration of the ion $HOOC—CBr_2—COO^-$, the specific rate being 1.88×10^{-4} at $25°$.[65] The rate of carbon dioxide production is not affected by the presence of bromine, but the product becomes largely tribromacetic acid, together with an amount of dibromacetic acid that varies inversely with the bromine concentration. These results are accounted for qualitatively if the $HOOC—CBr_2—COO^-$ loses CO_2 to form $[HOOC—CBr_2]^-$ in a rate-determining step. The proportion of dibromacetic acid in the product then depends upon competition between two reactions of this ion, one with acid, the other with bromine.

The analogous decompositions of α-nitroacetic acid and of α-nitroisobutyric acid[66] have rates that are proportional to the concentration of the ion $[O_2N—CR_2—CO_2]^-$ and are nearly the same for the two substances ($k = 0.000982$ for nitroacetate ion and 0.001716 for nitroisobutyrate ion at $17.84°$). The presence of bromine leaves the rate unaltered within 3 per cent, but the product is exclusively the bromnitromethane derivative although

[65] Muus, *J. Phys. Chem.*, **39**, 343 (1935); **40**, 121 (1936).
[66] Pedersen, *J. Phys. Chem.*, **38**, 559 (1934).

nitro-i-propane is not brominated under the prevailing conditions. The reaction intermediate is again formed by loss of carbon dioxide and is $[O_2N—CR_2]^-$.

A number of other carboxylate ions carrying strongly electron-attracting groups lose carbon dioxide in similar first-order reactions.[67] This is known to be the case with trichloracetate ion, with tribromacetate ion, with $C_6H_5—C\equiv C—CO_2^-$, and with $HOOC—CH_2—COO^-$. In all except the last case the neutral acid does not react, but malonic acid reacts about five times as fast as its singly charged ion, and the doubly charged ion shows no detectable reaction.

All these reactions that produce carbon dioxide reverse the process by which the carbanion of the Grignard reagent adds to carbon dioxide. They are closely related to the iodoform reaction

$$CH_3 - C\overset{O}{\underset{Cl_3}{<}} + OH^- \rightarrow CH_3C\overset{O}{\underset{OH}{<}} + [Cl_3]^- \qquad (LXII)$$
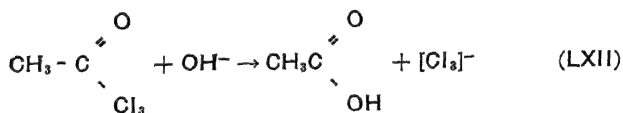
which is a displacement of carbanion by hydroxyl instead of a spontaneous separation, and to the interesting reaction

$$Cl_2C_6H_3CHO + OH^- \rightarrow Cl_2C_6H_4 + HCO_2^- \qquad (LXIII)$$
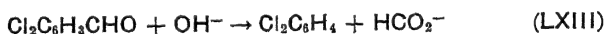
which 2,6-dichlorbenzaldehyde undergoes in lieu of the Cannizaro when it is treated with strong alkali.[68] A similar fission

$$\left[C_6H_5C\overset{O}{\underset{}{<}} - CH_2 - N\overset{CH - CH}{\underset{CH = CH}{<}}CH \right]^+ + OH^- \rightarrow C_6H_5C\overset{O}{\underset{OH}{<}} +$$
$$CH_2NC_5H_5 \qquad (LXIV)$$
$$CH_2NC_5H_5 + HA \rightarrow [CH_3NC_5H_5]^+ + A^- \qquad (LXV)$$
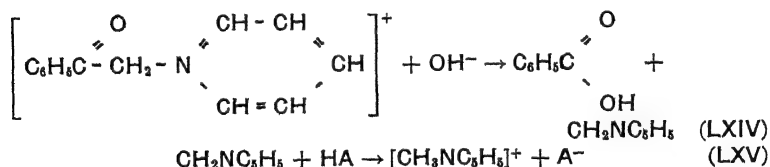
depends upon the electron-attracting property of the pyridine ring.[69] The reaction is favored by electron-attracting substituents in the phenyl group, being thirty times faster with the p-nitro derivative.

[67] FAIRCLOUGH, *J. Chem. Soc.*, 1186 (1938).

[68] LOCK, *Ber.*, **66B**, 1527 (1933).

[69] KRÖHNKE and HEFFE, *Ber.*, **70B**, 864 (1937).

The Hydrolysis of Amides.[70]—The hydrolysis of acetamide in dilute acid solutions satisfies the equation[70b]

$$v = k[\text{CH}_3\text{CONH}_3{}^+] = \frac{kc[\text{OH}_3{}^+]}{K + [\text{OH}_3{}^+]} \tag{34}$$

with c the stoichiometric concentration of acetamide and K the known ($\text{p}K = -0.50$) acidity constant of its conjugate acid $\text{CH}_3\text{CONH}_3{}^+$. According to this equation the specific rate v/c should approach the upper limit k as the acid concentration increases; actually, the rate goes through a maximum and decreases at higher acid concentrations. The same kind of maximum appears in the reactions of formamide and of propionamide. The data of Table V on the hydrolysis of formamide

TABLE V.—ACID-CATALYZED HYDROLYSIS OF FORMAMIDE[70d]
Catalyst HCl

м..................	2	4	5	6	7	8	9.5
$10^4 k$..................	2.28	4.42	4.84	5.12	4.98	4.50	3.53

Catalyst H₂SO₄

м..................	2	2.9	3.5	4.5	5.0	6.0	8.0
$10^4 k$..................	3.00	4.20	4.50	4.78	4.81	4.28	3.11

by hydrochloric and by sulfuric acid are typical. Above the maximum the rates agree reasonably with the equation

$$v \propto a^2{}_{\text{H}_2\text{O}} \tag{35}$$

which suggests that two molecules of water are involved in the rate-determining step. The medium effect in these concentrated acid solutions may, however, be so large as to render uncertain any conclusions of this sort.

The rate at the maximum is forty-six times greater for formamide and 20 per cent greater for propionamide than for acetamide.[70d]

[70] (a) BENRATH, *Z. anorg. allgem. Chem.*, **151**, 53 (1926). (b) EULER and ÖLANDER, *Z. physik. Chem.*, **131**, 107 (1928). (c) TAYLOR, *J. Chem. Soc.*, 2741 (1930). (d) KRIEBLE and HOLST, *J. Am. Chem. Soc.*, **60**, 2976 (1938). (e) REITZ, *Z. Elektrochem.*, **44**, 693 (1938).

Anilide Formation.[71]—Dilute solutions of carboxylic acids in the solvent aniline are converted to anilides at a rate that is second order in the acid. The addition of picric, hydrochloric, or hydrobromic acid increases the rate and makes it first order in the carboxylic acid; thus for acetic acid (HA) with picric acid (HP) as catalyst the rate equation at 100° is

$$v = 1.22 \times 10^{-5}[HA]^2 + 3.9 \times 10^{-5}[HA][HP] \qquad (36)$$

These phenomena are strongly reminiscent of those encountered in esterification (page 357) and indicate that the reaction of the acetic acid is self-catalyzed (first term) but more effectively catalyzed by a stronger acid (second term). Hydrobromic and hydrochloric acids have about the same effectiveness as picric acid in this reaction as in the diazoamino rearrangement (page 286) and, for the same reason, the leveling effect of the basic solvents. The rates of reaction of various carboxylic acids parallel their rates of esterification, *i.e.*, formic, very fast; acetic, 3.9×10^{-5}; propionic, 2.4×10^{-5}; n-butyric, 1.44×10^{-5}; i-butyric, 0.61×10^{-5}.

The Reactions of Acid Chlorides and Anhydrides.—The reactions of acid chlorides and anhydrides differ from those of esters in the way which would be predicted from the fact that these are combinations of acyl groups with less nucleophilic groups than the alkyloxy group of the ester. For this reason the addition of a nucleophilic reagent to the carbonyl carbon of R—CO—Cl should be easier than with R—CO—O—R, as should also be the rupture into R—CO+ and Cl−.

No acid catalysis has been observed in the reactions of acid chlorides.[72] This is in agreement with the considerations just cited, since the electron-attracting halogen should make the oxygen less basic, whereas the increased reactivity makes an acid catalysis dispensable. Whether there is a basic catalysis does not appear from the existing data. The Schotten-Baumann method of treating an alkaline aqueous solution of alcohol or amine with benzoyl chloride appears to be one, but the reaction is heterogeneous and the kinetics have not been investigated.

[71] GOLDSCHMIDT and WACHS, *Z. physik. Chem.*, **24**, 353 (1897). GOLDSCHMIDT and BRÄUER, *Ber.*, **39**, 97 (1906).

[72] OLIVIER and BERGER, *Rec. trav. chim.*, **46**, 861 (1927).

When an acyl chloride reacts with water or alcohol in large excess, the reaction is of the first order; when both chloride and alcohol are solutes in dilute solution in ether, it is of the second order in alcohol and of the first in acid chloride.[73]   The solvent exerts a pronounced and important effect as the following specific rates (times 10^5 and with the concentrations in mole fractions) for the reaction of benzoyl chloride with ethanol indicate[73b]: in ethyl ether, 2.2; *n*-butyl ether, 3.0; ethyl acetate, 4.4; acetone, 11.3; anisole, 13.3; nitrobenzene, 14; *n*-butyl chloride, 15; benzene, 17; chlorbenzene, 17; hexane, 19; carbon tetrachloride, 20; dimethylaniline, 58.   The value of tertiary amines as solvents for this reaction has been known and utilized for preparative purposes for a long time and has been attributed to a reactive intermediate of the type $[C_6H_5—N(CH_3)_2—CO—C_6H_5]^+ + Cl^-$. This may be a factor, but the quantitative data do not suffice to prove it since the ratio of the rate of reaction in dimethylaniline to that in carbon tetrachloride is only one-third of the ratio of the rate in carbon tetrachloride to that in ether.

The hydrolysis of acetic anhydride in aqueous solution shows little if any acid catalysis[72]; in the solvent acetic acid there is pronounced catalysis both by acids and by bases (page 285).

[73] (a) Norris, Fasce, and Staud, *J. Am. Chem. Soc.*, **57**, 1415 (1935). (b) Norris and Haines, *ibid.*, **57**, 1425 (1935).   (c) Ashdown, *ibid.*, **52**, 268 (1930).

CHAPTER XII

ATOM AND RADICAL REACTIONS: OTHER
REDOX REACTIONS

Chain Reactions.—The reaction in the gas phase

$$H_2 + I_2 \rightleftharpoons 2HI \tag{I}$$

is unaffected by external conditions other than temperature and is insensitive to catalytic effects of any sort. Its kinetics are bimolecular, and the process may be satisfactorily interpreted as a simple changing of partners (page 135).

The reaction of hydrogen with chlorine has entirely different properties. No reaction occurs in the absence of an external stimulus, but the absorption of light or of X rays, the action of gaseous ions, or the introduction of sodium atoms leads to an amount of reaction that is out of all proportion to the magnitude of the stimulus. One light quantum[1] or one sodium atom[2] may induce the formation of as many as a thousand molecules of hydrogen chloride. Such effects may be accounted for by what is called a *chain mechanism*.[1,3] The light quantum or the sodium atom produces atomic chlorine by the reactions

$$Cl_2 + h\nu \rightarrow 2Cl \tag{II}$$
$$Na + Cl_2 \rightarrow NaCl + Cl \tag{III}$$
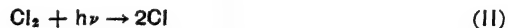
and this reacts as follows:

$$Cl + H_2 \rightarrow HCl + H \tag{IV}$$
$$H + Cl_2 \rightarrow HCl + Cl \tag{V}$$

The sequence (IV), (V) produces two molecules of HCl and regenerates an atom of chlorine, which may initiate a repetition of the cycle or chain. The atomic chlorine and hydrogen are, therefore, called *chain carriers*. Obviously the chain can con-

[1] BODENSTEIN, *Z. physik. Chem.*, **85**, 346 (1913).
[2] BOGDANDY and POLANYI, *Z. Elektrochem.*, **33**, 554 (1927).
[3] NERNST, *Z. Elektrochem.*, **24**, 335 (1918).

tinue until something happens to a carrier which does not produce another carrier to take its place. If such "chain-breaking reactions" are sufficiently rare, the large number of hydrogen chloride molecules produced by the initial formation of one chlorine atom is immediately accounted for.

The chain might conceivably be broken by any of the combination processes

$$
\begin{array}{ll}
2H \rightarrow H_2 & \text{(VI)} \\
2Cl \rightarrow Cl_2 & \text{(VII)} \\
H + Cl \rightarrow HCl & \text{(VIII)}
\end{array}
$$

These are unlikely because they involve collisions between two molecules present in very low concentration, whereas the chain-propagation reactions (IV) and (V) involve a collision of a rare molecule with one present in large concentration. In addition, the combination of atoms (although not necessarily that of radicals) can occur only if a simultaneous collision with a third body dissipates the energy of the reaction. The chain may also be broken by adsorption of a carrier on the wall of the container, where it must eventually combine with another atom or radical but finds leisure to do so. It may finally be broken by the reaction of a carrier with an impurity to form products that are inactive as carriers. Since the concentration of the carriers is always minute, the concentration of chain-breaking impurity need only be small to exert a profound effect on the rate of reaction. If one carrier atom may produce a thousand molecules of hydrogen chloride, the removal of one carrier molecule may inhibit the formation of a thousand molecules. Such an inhibition is in fact produced by traces of oxygen in the hydrogen-chlorine reaction. When the formation of carriers is continued by steady illumination with light of suitable frequency, the inhibiting oxygen is eventually used up by reaction with the carriers, and the reaction then speeds up greatly. The reaction under these conditions shows a "period of induction," a period of slow or negligible reaction during which the oxygen is eliminated, after which a rapid reaction takes place. Neither the action of sodium in inducing the reaction nor that of oxygen in inhibiting it should properly be called catalytic since the substances are consumed as a result of their action.

Autoxidations.—Many if not all those reactions with molecular oxygen, which take place at ordinary temperatures without the accompaniment of the phenomena of combustion and which were entitled autoxidations in the days when the word oxidation meant reaction with oxygen and nothing else, exhibit the kind of sensitivity to inducing and inhibiting agents that is so characteristic a property of the hydrogen-chlorine reaction. A classical example is the reaction of sulfite ion with oxygen to form sulfate ion. Amounts of copper ion of the order of 10^{-12}M produce a measurable acceleration of the reaction,[4] and small amounts of oxidizable organic substances, such as primary and secondary alcohols, profoundly inhibit it. Tertiary alcohols, which are not easily oxidized, have no such effect.[4b] The reaction is accelerated by ultraviolet light, and the number of molecules that react per light quantum is of the order of tens of thousands; consequently, a chain mechanism is possible. As the photochemical reaction is inhibited by the same substances that inhibit the reaction in the absence of light, the same chain must be involved in both cases, the light acting merely as a chain starter.[5] Finally, it has been shown[6] that benzaldehyde is formed when benzyl alcohol is used as an inhibitor in the sulfite autoxidation, and acetone appears when i-propyl alcohol is used. Consequently, the inhibitor breaks the chain by a process that involves its own oxidation.

The nature of the radicals involved in the oxidation offers much scope for speculation. A reasonable chain-starting process[7] is the attack on a sulfite or a bisulfite ion of a cupric ion or of some similar oxidant forming the odd electron substance SO_3^- or HSO_3. This and the hydroxyl radical OH may then carry on a chain. A study of the dependence of the rate on the acidity of the solution[8] has shown that the rate parallels the concentration of SO_3^- when the concentration of inhibitor is very small, but that it parallels the product $[HSO_3^-][SO_3^-]$ when a

[4] (a) Titoff, *Z. physik. Chem.*, **45**, 641 (1903). (b) Bigelow, *ibid.*, **26**, 493 (1898).

[5] Bäckström, *J. Am. Chem. Soc.*, **49**, 1460 (1927).

[6] Alyea and Bäckström, *J. Am. Chem. Soc.*, **51**, 90 (1929).

[7] Haber and Willstätter, *Ber.*, **64**, 2844 (1931).

[8] Bäckström. *Z. physik. Chem.*, **B25**, 122 (1934).

relatively large concentration of inhibitor is present. This effect suggests[8] the following system of reactions in which X is the inhibitor:

$$Cu^{++} + SO_3^- \rightleftharpoons Cu^+ + SO_3^- \tag{IX}$$
$$SO_3^- + O_2 \rightarrow SO_5^- \tag{X}$$
$$SO_5^- + HSO_3^- \rightarrow HSO_5^- + SO_3^- \tag{XI}$$
$$SO_5^- + X \rightarrow noncarriers \tag{XII}$$
$$HSO_5^- + SO_3^- \rightarrow HSO_4^- + SO_4^- \tag{XIII}$$
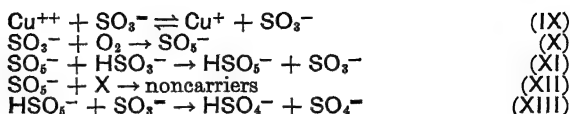
which leads to the expression

$$v = \frac{2k_1 k_2 k_3 [Cu^{++}][SO_3^-][HSO_3^-][O_2]}{k_{-1} k_3 [Cu^+][HSO_3^-] + \{k_{-1} k_4 [Cu^+] + k_2 k_4 [O_2]\}[X]} \tag{1}$$

When the second term in the denominator may be neglected, the concentration of HSO_3^- cancels, and the only pH dependent factor is $[SO_3^-]$; when the first term may be neglected, the rate is proportional to $[HSO_3^-][SO_3^-]$. The intermediates have the following structures:

$$
\begin{bmatrix} \begin{smallmatrix} & \cdot\bar{O}\cdot & \\ & | & \\ \cdot\bar{O}- & S\cdot & \\ & | & \\ & \cdot O\cdot & \end{smallmatrix} \end{bmatrix}^-
\quad
\begin{bmatrix} \begin{smallmatrix} & \cdot\bar{O}\cdot & \\ & | & \\ \cdot\bar{O}- & S- & \bar{O}- & \bar{O}\cdot \\ & | & \\ & \cdot O\cdot & \end{smallmatrix} \end{bmatrix}^-
\quad
\begin{bmatrix} \begin{smallmatrix} & \cdot\bar{O}\cdot & \\ & | & \\ \cdot\bar{O}- & S- & \bar{O}- & \bar{O}- & H \\ & | & \\ & \cdot O\cdot & \end{smallmatrix} \end{bmatrix}^-
$$
$$(A) \qquad\qquad (B) \qquad\qquad\qquad (C)$$
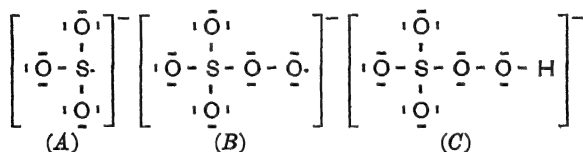
The substance (A) is a very probable intermediate in the oxidation of sulfite ion to dithionate ion $S_2O_6^-$, consequently, there is independent evidence for reactions of the type of (IX); reaction (X) is exactly paralleled in the triphenylmethyl autoxidation; reaction (XI) is the transfer of a hydrogen atom, *i.e.*, a radical displacement on hydrogen; substance (C) is not a radical, but a known substance, Caro's acid, of sufficiently powerful oxidizing properties to account for reaction (XIII); reaction (XII) may be any one of a variety of chain-breaking processes involving the oxidation of an inhibitor.

The Autoxidation of Triphenylmethyl.[9]—Hexaphenylethane in chloroform solution is oxidized by iodine to triphenylmethyl iodide at a rate which is independent of the iodine concentration

[9] (a) ZIEGLER, EWALD, and ORTH, *Ann.*, **479**, 277 (1930). (b) ZIEGLER and ORTH, *Ber.*, **65**, 628 (1932). (c) ZIEGLER and EWALD, *Ann.*, **504**, 162 (1933).

and which corresponds nearly enough to the colorimetrically estimated rate of dissociation of the ethane into triphenylmethyl. The rate of reaction with oxygen is two to four times faster than that with iodine and shows a somewhat less than first-order dependence on the concentration of oxygen and a more than first-order dependence on the concentration of hexaphenylethane. The last effect excludes any interpretation that involves either a direct reaction of oxygen with ethane parallel to that with the radical or a reaction of oxygen with the radical the rate of which is comparable to that of the dissociation of the ethane. All the effects are, however, consistent with the sequence of reactions

$$(C_6H_5)_3C - C(C_6H_5)_3 \rightleftharpoons 2(C_6H_5)_3C\cdot \qquad (XIV)$$

$$(C_6H_5)_3C\cdot + O_2 \rightarrow (C_6H_5)_3C - \bar{O} - \bar{O}\cdot \qquad (XV)$$

$$(C_6H_5)_3C - \bar{O} - \bar{O}\cdot + (C_6H_5)_3C - C(C_6H_5)_3 \rightarrow (C_6H_5)_3C - \bar{O} - \bar{O} - C(C_6H_5)_3 +$$
$$(C_6H_5)_3C\cdot \quad (XVI)$$
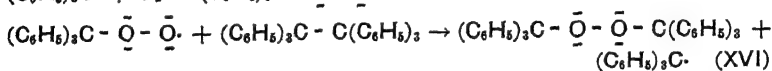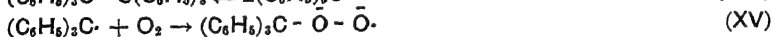
The interpretation is abundantly confirmed by the fact that the oxidation of hexaphenylethane induces a chain oxidation of anisaldehyde, styrene, dimethylfulvene, and the like, in which the number of molecules of the latter oxidized may be as many as 65 for each molecule of hexaphenylethane reacting. The triphenylmethyl radical plays the same part in the induced oxidation that the sodium atoms do in the hydrogen-chlorine reaction.

Autoxidation of Aldehydes.—The addition of a radical to an oxygen molecule which appears in reactions (X) and (XV) may also account for the ferrous ion catalyzed autoxidation of benzaldehyde to perbenzoic acid.[10] A reasonable mechanism[11] is the following:

$$\overset{H}{\underset{|}{C_6H_5 - C}} = \bar{O} \cdot + Fe^{+++} \rightarrow C_6H_5 - \dot{C} = \bar{O} \cdot + Fe^{++} + H^+ \qquad (XVII)$$

$$C_6H_5 - \dot{C} = \bar{O} \cdot + O_2 \rightarrow C_6H_5 - \underset{\underset{\bar{O}}{\|}}{C} - \bar{O} - \bar{O}\cdot$$

$$C_6H_5 - \underset{\underset{\bar{O}}{\|}}{C} - \bar{O} - \bar{O}\cdot + C_6H_5 - \underset{\underset{H}{|}}{C} = \bar{O}\cdot \rightarrow C_6H_5 - \underset{\underset{\bar{O}}{\|}}{C} - \bar{O} - \bar{O} - H + C_6H_5 - \dot{C} = \bar{O}\cdot$$
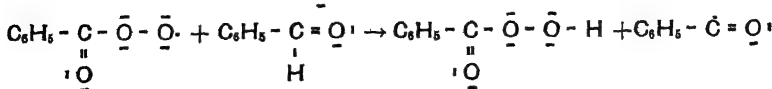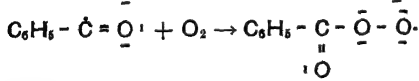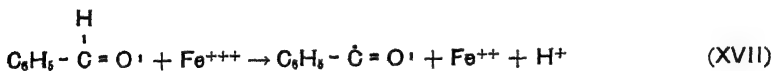
[10] WIELAND and RICHTER, *Ann.*, **486**, 226 (1931).
[11] RICE and RICE, "The Aliphatic Free Radicals," Baltimore, 1935, p. 179.

The autoxidation of benzaldehyde is powerfully inhibited by certain phenylated olefins. Thus the olefin (D) in the amount

$$C = C \qquad C = O$$

(D) (E)

$$C - C$$
$$OH \ OH$$
(F)
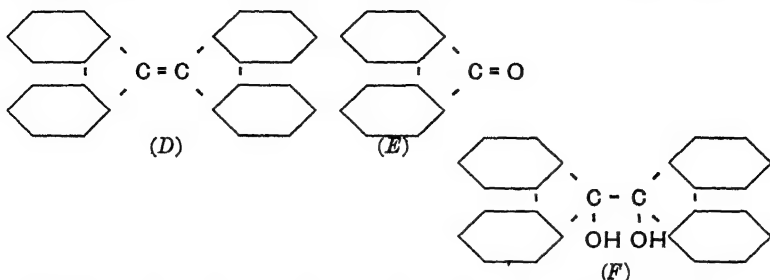
of 1.3 per cent of the weight of the aldehyde reduces the rate of autoxidation of benzaldehyde sixteen-fold and is itself simultaneously oxidized to fluorenone (E).[12] The coupling of the two oxidations does not involve the action of perbenzoic acid on (D), as these substances do not react under the prevailing conditions; it must involve the chain-carrying radicals of the aldehyde oxidation. The much slower autoxidation that (D) undergoes in the absence of aldehyde is itself a chain process, since the reaction may induce an autoxidation of dioxane when the latter is used as the solvent. The glycol (F) is not involved in these chains, since it is not attacked when present in the oxidizing mixtures and does not inhibit the autoxidation of benzaldehyde.

Other Oxygen-induced Olefin Reactions.—The autoxidation of acrolein is powerfully inhibited by a variety of oxidizable organic substances, notably by hydroquinone and pyrogallol.[13] These are frequently called *antioxidants*, and under this name inhibitors of oxidation and of oxygen-induced reactions have had a wide technical importance. The same substances that inhibit the autoxidation are found[13] also to inhibit the otherwise easy polymerization of acrolein. It seems, therefore, probable that the radicals involved in the oxidation can also induce a polymerization, probably by way of the formation of a radical of the type $[R_2\bar{C} - \dot{C}R_2]^-$, and its condensation according to[14]

$$[R_2\bar{C} - \dot{C}R_2]^- + R_2C = CR_2 \rightarrow [R_2\bar{C} - CR_2 - CR_2 - \dot{C}R_2]^- \quad \text{(XVIII)}$$

[12] WITTIG and LANGE, *Ann.*, **536**, 266 (1938).
[13] MOUREU and DUFRAISSE, *Chem. Rev.*, **3**, 113 (1926).
[14] DOSTAL and MARK, *Angew. Chem.*, **50**, 348 (1937).

forming a new radical that may condense further. The polymerization stops by disappearance of the odd electron through combination of radicals, by exhaustion of material, or simply because the entropy of activation decreases with increasing degree of polymerization (page 126).

The addition of sodium bisulfite to an olefin occurs only in the presence of oxygen or an oxidizing agent[15] and forms products analogous in structure to those produced in the oxygen-induced addition of bromine (page 375). Thus $CH_3-CH=CH_2$ yields $[CH_3-CH_2-CH_2SO_3]^-$ rather than the isopropyl derivative. A reasonable reaction course involves the radical SO_3^- (page 371)

(XIX)

(XX)
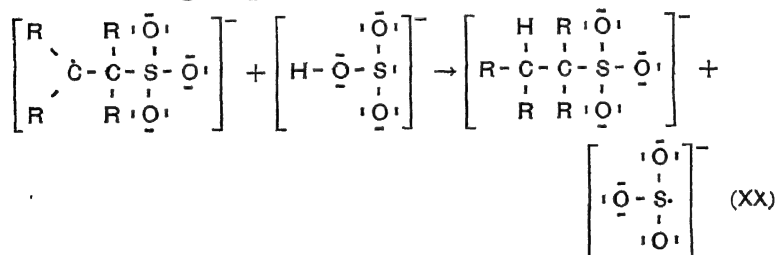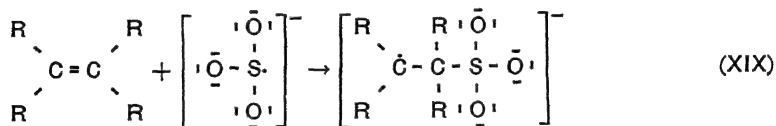
The olefin sulfonic acid, which is the chief product from styrene, can be attributed to the transfer of a hydrogen atom from the intermediate (G) to some oxidizing agent, possibly Caro's acid, which is an intermediate in the sulfite oxidation.

(G)
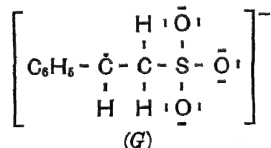
The Peroxide Effect in the Olefin HBr Reaction.[16]—Under the usual conditions of synthetic operations, allyl bromide, $CH_2=$

[15] KHARASCH, MAY, and MAYO, *J. Org. Chem.*, **3**, 175 (1938).

[16] (a) KHARASCH and MAYO, *J. Am. Chem. Soc.*, **55**, 2468 (1933). (b) KHARASCH, McNAB, and MAYO, *ibid.*, **55**, 2521; 2531 (1933).

CH—CHBr, reacts with hydrogen bromide to yield a mixture of 1,2- and 1,3-dibrompropanes of variable composition. If the reaction is carried out with carefully purified materials under conditions of rigid exclusion of oxygen and of the peroxides which are always present in olefins that have been exposed to the air, the product consists of the 1,2 compound to the extent of about 90 per cent. An occasional experiment may yield a variant result for no obvious reason, but the addition of a small amount of the antioxidant hydroquinone or diphenylamine leads to a product in which the 1,2 compound amounts without exception to 90 per cent. Ferric bromide also favors the 1,2 compound to a pronounced extent. On the other hand, the deliberate addition of oxygen, and still more that of benzoyl peroxide, leads to a 90 per cent formation of the 1,3 compound.

Propylene reacts with hydrogen bromide under ordinary conditions to form i-propyl bromide, following what is often called Markonikoff's rule. Exclusion of oxygen or addition of antioxidants does not alter the result, but benzoyl peroxide leads to formation of practically pure n-propyl bromide. Many other examples of effects of this sort in the reaction of hydrogen bromide with olefins have been observed, but they never appear in the addition of hydrogen chloride, of sulfuric acid, of nitric acid, or of water to the olefinic linkage. These always lead to a single product the structure of which corresponds to that produced with hydrogen bromide under antioxidant conditions. As a number of them are known (page 292) to involve a proton addition, it is a reasonable hypothesis that the hydrogen bromide addition under antioxidant conditions also involves the sequence

$$CH_3 - CH = CH_2 + H - \bar{Br} \rightarrow [CH_3 - CH - CH_3]^+ + Br^- \quad \text{(XXI)}$$

$$[CH_3 - CH - CH_3]^+ + Br^- \rightarrow CH_3 - CHBr - CH_3 \quad \text{(XXII)}$$
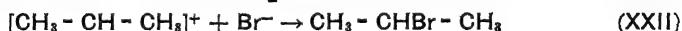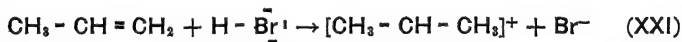
This is supported by the favorable effect of ferric bromide, which by virtue of its affinity for bromide ion must increase the strength of hydrobromic acid.

The variant reaction in the presence of oxygen or peroxides may then depend on an atom reaction of the type[17]

[17] KHARASCH, ENGELMANN, and MAYO, *J. Org. Chem.*, **2**, 288; 400 (1937).

$$CH_3 - CH = CH_2 + \cdot\bar{Br} \, \mathbf{\cdot} \rightarrow CH_3 - \dot{C}H - CH_2Br \qquad (XXIII)$$

$$CH_3 - \dot{C}H - CH_2Br + H - Br \rightarrow CH_3 - CH_2 - CH_2Br + \cdot \bar{Br}\cdot \quad (XXIV)$$
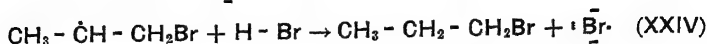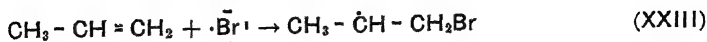
Other Oxygen-induced Reactions Involving Bromine.—Iso·
stilbene, which is unaffected by hydrogen bromide in the dark or
in the light provided that antioxidants are present, undergoes a
cis-trans rearrangement to stilbene under the influence of hydro-
gen bromide in the light if oxygen is present and even in the dark
if peroxides are added. The process probably involves the
addition of a bromine atom

$$C_6H_5 - CH = CH - C_6H_5 + \cdot\bar{Br} \, \mathbf{\cdot} \rightarrow C_6H_5 - \dot{C}H - CHBr - C_6H_5 \quad (XXV)$$
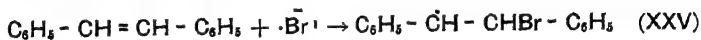
rotation about the carbon-carbon link, which no longer possesses
the double-bond resistance to rotation, and elimination of the
bromine atom.[18]   Chlorstilbene is also isomerized by hydrogen
bromide in the presence of oxygen and light.

The rearrangement of $CH_3COCHBrCOOC_2H_5$ to CH_2Br-
$COCH_2COOC_2H_5$ is accelerated by hydrogen bromide and in
the presence of hydrogen bromide is still further accelerated by
air, by peroxides, or by illumination.[19]

The bromination of toluene in the side chain is accelerated by
benzoyl peroxide or by ascaridol (a cyclic terpene peroxide of
natural origin) either in the dark or in the light, and the photo-
chemical reaction is retarded by exclusion of oxygen.   Both
peroxide-catalyzed and photochemical reactions are inhibited by
small amounts of nitrosobenzene or amyl nitrite.[20]   The side-
chain reaction competes with the nuclear bromination which is
not photochemical, not affected either by peroxides or by anti-
oxidants, but is strongly favored by substances with an affinity
for bromide ion and doubtless has a positive bromine-ion inter-
mediate (page 312).

The addition of bromine to phenanthrene is inhibited by the
antioxidants hydroquinone and diphenylamine;[21] it induces a

[18] KHARASCH, MANSFIELD, and MAYO, *J. Am. Chem. Soc.*, **59**, 1155 (1937);
TAYLOR and MURRAY, *J. Chem. Soc.*, 2078 (1938).

[19] KHARASCH, STERNFELD and MAYO, *J. Am. Chem. Soc.*, **59**, 1655 (1937).

[20] KHARASCH, WHITE, and MAYO, *J. Org. Chem.*, **3**, 33 (1938).

[21] PRICE, *J. Am. Chem. Soc.*, **58**, 1834 (1936).   PRICE and THORPE, *ibid.*,
60, 2839 (1938).

bromination of dioxane. The reaction of bromine with anthracene induces the addition of bromine to phenanthrene or the bromination of dioxane.

All these varied phenomena are accounted for by the hypothesis that the reactions are chain reactions with bromine atoms as the carriers, that oxygen or peroxides act as chain starters, especially in the light, and that antioxidants suppress the chain-starting process. The details of the steps are obscure and probably vary from case to case; in fact, oxygen may even retard rather than accelerate a bromine addition. This is the case with the addition of bromine to cinnamic acid in carbon tetrachloride.[22]

The Autoxidation of Phenols: Nonenzymatic Processes.—The autoxidation of ortho and para dihydric phenols shows a pronounced acceleration by copper or manganous ions or by an increase in pH. The reaction products are complex in the case of hydroquinone or catechol, and the problem is materially simplified by the use of durohydroquinone.[23] This reacts accurately according to the stoichiometric equation

$$\text{HO} - \underset{\underset{\text{CH}_3}{|}\ \underset{\text{CH}_3}{|}}{\overset{\overset{\text{CH}_3}{|}\ \overset{\text{CH}_3}{|}}{\bigcirc}} - \text{OH} + \text{O}_2 \rightarrow \text{O} = \underset{\underset{\text{CH}_3}{|}\ \underset{\text{CH}_3}{|}}{\overset{\overset{\text{CH}_3}{|}\ \overset{\text{CH}_3}{|}}{\bigcirc}} = \text{O} + \text{H}_2\text{O}_2 \quad \text{(XXVI)}$$
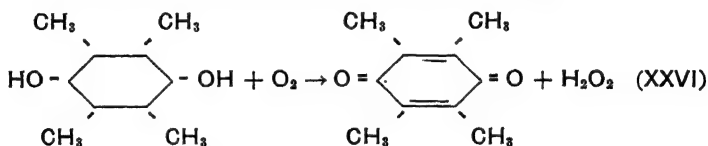
The rate law (Q = quinone, H_2Q = hydroquinone)

$$v = k_1[\text{H}_2\text{Q}][\text{O}_2][\text{OH}^-]^2 + k_2[\text{H}_2\text{Q}][\text{Q}][\text{OH}^-]^2 \quad (2)$$

shows the presence of two parallel reactions. The first may formally be represented as the transfer of two electrons from the doubly charged anion of the hydroquinone Q^- to an oxygen molecule with the formation of quinone and peroxide ion O_2^-; the second might be attributed to a rate-determining process

$$Q^- + Q \rightarrow 2Q^- \quad \text{(XXVII)}$$

The pronounced metallic-ion catalysis shows, however, that the reactions must follow a more involved course. The indication that the semiquinone with its odd electron is involved is reminiscent of the autoxidation of triphenylmethyl (page 371).

[22] BAUER and DANIELS, *J. Am. Chem. Soc.*, **56**, 2014 (1934).
[23] JAMES and WEISSBERGER, *J. Am. Chem. Soc.*, **60**, 98 (1938).

The rates of autoxidation of hydroquinone and of the mono-, di-, and tri-methylhydroquinones[24] show the same dependence on pH and on oxygen pressure and the same catalysis by cupric ion that the tetramethyl derivative does. The reaction leads to complex condensation products, and quinone and hydrogen peroxide can be detected only in traces. The probable explanation is that the reaction

$$C_6H_4O_2 + H_2O_2 \rightarrow C_6H_3O_2(OH) + H_2O \qquad (XXVIII)$$

produces a hydroxyquinone, which is detectable in traces in the reaction product and which is known to condense rapidly to materials of high molecular weight.

The autoxidation of trimethylhydroquinone shows the same kind of catalysis by the quinone that is observed in the tetramethyl compound; the less highly methylated substances do not. If the effect is present with these but masked in some way, the well-known inhibition of the autoxidation of hydroquinone by sulfites, so important in the stabilization of photographic developers, may depend upon the reaction

$$O = \left\langle \bigcirc \right\rangle = O + HSO_3^- \rightarrow \left[HO \left\langle \bigcirc \right\rangle - OH \right]^- \qquad (XXIX)$$
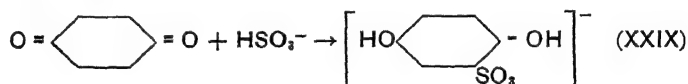
This reaction is impossible in the case of durohydroquinone, and the autoxidation of this substance is not inhibited by sulfite.

Enzymatic Autoxidation of Phenols.[25]—The autoxidation of catechol in the presence of the enzyme tyrosinase forms orthoquinone. There is no evidence that hydrogen peroxide is formed or otherwise concerned in the process and much evidence that it is not. The quinone undergoes a reaction accelerated both by hydroxyl ions and by catechol the stoichiometric course of which is

$$2C_6H_4O_2 + H_2O \rightarrow C_6H_4(OH)_2 + C_6H_3O_2(OH) \qquad (XXX)$$
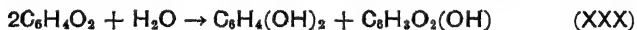
and the regenerated catechol reacts with oxygen again, whereas the hydroxyquinone condenses to substances of high molecular weight and unknown composition.

[24] JAMES, SNELL, and WEISSBERGER, *J. Am. Chem. Soc.*, **60**, 2084 (1938).
[25] (a) DAWSON and NELSON, *J. Am. Chem. Soc.* **60**, 250 (1938). (b) WAGREICH and NELSON, *ibid.*, 1545. (c) DAWSON and LUDWIG, *ibid.*, **60**, 1617 (1938). (d) BORDNER and NELSON, *ibid.*, **61**, 1507 (1939).

The enzymatic autoxidation of catechol induces an autoxidation of phenol or cresol, which does not take place or takes place at a greatly reduced rate when the enzyme and oxygen act on the monohydric phenol in the absence of catechol. Under the prevailing conditions neither orthobenzoquinone nor hydrogen peroxide attacks phenol. The rate is apparently proportional to the concentration of catechol, being decreased by substances that react with catechol or orthoquinone and increased by reducing agents that convert the quinone to catechol.

Combustion: Branching Chains.—The interpretation of the kinetics of combustion reactions has required the assumption of "branching" radical chains, *viz.*, chains containing reactions in which one carrier forms two or more. Thus the following reaction system accounts satisfactorily for the combustion of hydrogen:[26] Hydrogen atoms produced by the thermal dissociation of molecular hydrogen react by the chain-branching process

$$H + O_2 \rightarrow HO + O \qquad \text{(XXXI)}$$

in which one hydrogen atom produces two active chain carriers. These react according to

$$HO + H_2 \rightarrow H_2O + H \qquad \text{(XXXII)}$$
$$O + H_2 \rightarrow OH + H \qquad \text{(XXXIII)}$$

thus yielding two hydrogen atoms and a hydroxyl radical for each hydrogen reacting in reaction (XXXI). The chain carriers are not merely regenerated, their number increases as a result of the cycle; consequently, the rate of reaction increases rapidly. Such a process can obviously account for an explosive reaction; it is difficult to see how any other can.

Radical Chains in Cracking Reactions.—If the gaseous reaction products obtained by heating tetramethyl lead are led rapidly over a thin, clean, mirrorlike deposit of lead, zinc, or the like, the metal is removed with the formation of gaseous metallic compounds, from which the metal can be regenerated by heating.[27] The material formed from zinc has been shown by its

[26] Lewis and von Elbe, "Combustion, Flames and Explosions of Gases," Cambridge, 1938.

[27] Paneth and Hofeditz, *Ber.*, **62**, 1335 (1929).

melting and boiling points to be dimethyl zinc, $Zn(CH_3)_2$. There can be little doubt, therefore, that the decomposition of tetramethyl lead forms methyl radicals. The property of removing metal mirrors is a very sensitive test for the presence of alkyl radicals and makes possible the study of these very reactive substances. For instance, the half life of the methyl radical is found to be 0.001 to 0.01 sec.

By the use of this technique it is found[28] that the thermal decomposition at temperatures from 750 to 950°c of a great many hydrocarbons, ketones, and ethers produces alkyl radicals. Less stable substances, such as ethylene oxide, azomethane, and azo-*i*-propane form radicals at temperatures as low as 450°. The same radicals with the same properties are also formed by the action of sodium vapor on gaseous alkyl and aryl halides (page 144).

The alkyl radicals have a powerful inducing action on the decomposition of carbon compounds.[29] When, for instance, a mixture of butane and mercury dimethyl is heated at a temperature (525°) at which the mercury compound decomposes, but at which pure butane is entirely stable, some 20 molecules of butane are decomposed for every molecule of mercury dimethyl that reacts. Similarly, the decomposition of one molecule of azomethane at 300° in the presence of acetaldehyde induces the decomposition of 30 molecules of the latter. The indication of a chain reaction is obvious and emphatic, and it is a reasonable hypothesis[28] to suppose that the thermal-decomposition reactions of carbon compounds in general depend upon radical chains of the same type initiated by the thermal rupture of a molecule of the reactant. The probable chain-propagating reactions are simple displacements of the radical type such as [30]

$$\underset{\underset{H}{|}}{\overset{\overset{H}{|}}{H-C\cdot}} + \underset{\underset{H}{|}}{\overset{\overset{H}{|}}{H-C}} - \underset{\underset{H}{|}}{\overset{\overset{H}{|}}{C}} - H \rightarrow \underset{\underset{H}{|}}{\overset{\overset{H}{|}}{H-C}} - H + \underset{\underset{H}{|}}{\overset{\overset{H}{|}}{\cdot C}} - \underset{\underset{H}{|}}{\overset{\overset{H}{|}}{C}} - H \qquad (XXXIV)$$
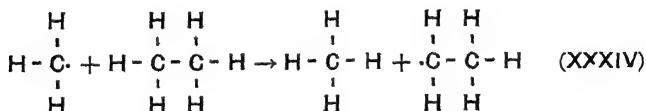
[28] RICE and RICE, "The Aliphatic Free Radicals," Baltimore, 1935.

[29] FREY, *Ind. Eng. Chem.*, **26**, 198 (1934). SICKMANN and ALLEN, *J. Am. Chem. Soc.*, **56**, 1251 (1934). ALLEN and SICKMANN, *ibid.*, 2031.

[30] RICE and TELLER, *J. Chem. Phys.*, **6**, 489 (1938).

or

$$
\begin{array}{cccc}
\overset{\displaystyle H}{\underset{\displaystyle H}{\cdot C}} - \overset{\displaystyle H}{\underset{\displaystyle H}{C}} - H
& + \;
H - \overset{\displaystyle H}{\underset{\displaystyle H}{C}} - \overset{\displaystyle H}{\underset{\displaystyle H}{C}} - H
\; \rightarrow \;
\overset{\displaystyle H}{\underset{\displaystyle H}{C}} = \overset{\displaystyle H}{\underset{\displaystyle H}{C}}
\; + \; H - H \; + \;
\cdot\overset{\displaystyle H}{\underset{\displaystyle H}{C}} - \overset{\displaystyle H}{\underset{\displaystyle H}{C}} - H
& \text{(XXXV)}
\end{array}
$$
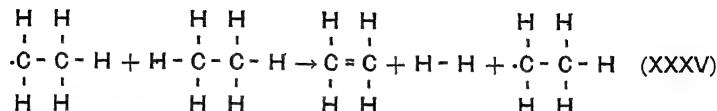
or addition reactions such as

$$
H - \overset{\displaystyle H}{\underset{\displaystyle H}{C}}\cdot \; + \; \overset{\displaystyle H}{\underset{\displaystyle H}{C}} = \overset{\displaystyle H}{\underset{\displaystyle H}{C}} \; \rightarrow \; H - \overset{\displaystyle H}{\underset{\displaystyle H}{C}} - \overset{\displaystyle H}{\underset{\displaystyle H}{C}} - \overset{\displaystyle H}{\underset{\displaystyle H}{C}}\cdot \qquad \text{(XXXVI)}
$$
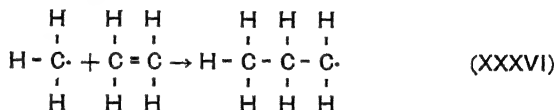
A possible chain-breaking reaction is the dismutation

$$
H - \overset{\displaystyle H}{\underset{\displaystyle H}{C}} - \overset{\displaystyle H}{\underset{\displaystyle H}{C}}\cdot \; + \; H - \overset{\displaystyle H}{\underset{\displaystyle H}{C}} - \overset{\displaystyle H}{\underset{\displaystyle H}{C}}\cdot \; \rightarrow \; H - \overset{\displaystyle H}{\underset{\displaystyle H}{C}} - \overset{\displaystyle H}{\underset{\displaystyle H}{C}} - H \; + \; \overset{\displaystyle H}{\underset{\displaystyle H}{C}} = \overset{\displaystyle H}{\underset{\displaystyle H}{C}} \qquad \text{(XXXVII)}
$$
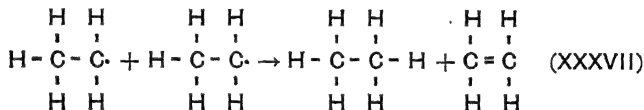
which is also a radical displacement on hydrogen.

The Photochemical Formation of Radicals.[31]—The photochemical decomposition of a carbonyl compound RCOR' in the gas phase yields different products according to the nature of the groups R and R'. With acetone and methyl ethyl ketone the products are CO and the three hydrocarbons R—R, R—R', and R'—R'. The presumption that this process involves the radicals R and R' is confirmed by the fact that the photochemical decomposition of the same substances in solution in a high-boiling paraffin hydrocarbon leads to the formation of R—H and R'—H while the high-boiling solvent becomes unsaturated. Evidently the radicals abstract hydrogen from the solvent molecules. Ketones with longer chains react differently, methyl-*n*-butyl ketone yielding acetone and propylene, although aldehydes RCOH yield only CO and RH.

Free Radicals in Solution: Oxidation of the Grignard Reagent and Reduction of Alkyl Halides.—The electrolysis of ethyl magnesium halide in ether solution[32] yields at the anode chiefly

[31] NORRISH, *Trans. Faraday Soc.*, **30**, 103 (1934). NORRISH and BAMFORD, *Nature*, **140**, 195 (1937).

[32] (a) EVANS and LEE, *J. Am. Chem. Soc.*, **56**, 654 (1934). (b) EVANS, LEE, and LEE, *ibid.*, **57**, 489 (1935). (c) EVANS and FIELD, *ibid.*, **58**, 720 (1936).

ethane and ethylene, and propyl magnesium halide yields propane and propylene. These products can be accounted for on the hypothesis that the electrolytic oxidation of the carbanion of the reagent yields alkyl radicals by the reaction

$$\left[\begin{array}{c} H\ H \\ H-C-C \\ H\ H \end{array}\right]^{-} \rightarrow H-\overset{H}{\underset{H}{C}}-\overset{H}{\underset{H}{C}}\cdot + e \qquad \text{(XXXVIII)}$$
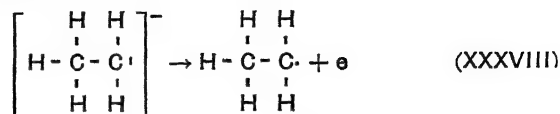
or, probably more accurately, by (page 146)

$$[(C_2H_5)_2MgI_2]^- \rightarrow 2C_2H_5 + MgI_2 + 2e \qquad \text{(XXXIX)}$$

The ethyl or propyl radicals then dismute to ethane and ethylene by equation (XXXVII) or to propane and propylene by a similar process.

The reaction of methylmagnesium iodide is especially indicative of the formation of radicals. Its electrolytic oxidation yields chiefly ethane when the concentration of the Grignard reagent is high, but much methane together with some ethylene and isobutylene is formed at lower concentrations. The amount of methane is much too large in proportion to the olefins to be accounted for by any dismutation process, and the substance is clearly produced by the same kind of attack of radical on the hydrogen of the solvent that is observed in the photochemical ketone decomposition (page 381). The decomposition of the ether solvent thus induced leads to the appearance of carbon dioxide in the reaction products. The other products of the oxidation are easily accounted for: the ethane can be attributed to the combination of two methyl radicals and the favorable effect of high concentration is consistent with such a bimolecular process, the isobutylene and some of the ethylene to a polymerization of CH_2 produced by a dismutation of CH_3, and the rest of the ethylene to the decomposition of the solvent.

The electrolytic reduction of ethyl iodide in alcoholic solution[33] appears to have as its initial step the reaction

$$C_2H_5I + e \rightarrow C_2H_5 + I^- \qquad \text{(XL)}$$

If it depended upon an attack of electrolytically produced hydrogen atoms, the relative amounts of hydrogen and organic reduc-

[33] PLUMP and HAMMETT, *Trans. Electrochemical Soc.*, **73**, 523 (1938).

tion products should be independent of the acidity of the solution, as this can affect only the rate of formation of atomic hydrogen and not the course of its subsequent reaction. Actually, the proportion of hydrogen increases rapidly with increasing acidity of the solution. The reaction products ethane, ethylene, and butane can be accounted for by the following reasonable reactions of the ethyl radical:

$$C_2H_5 + H^+ + e \rightarrow C_2H_6 \qquad \text{(XLI)}$$
$$2C_2H_5 \rightarrow C_4H_{10} \qquad \text{(XLII)}$$
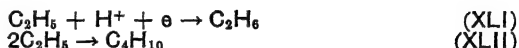
together with the dismutation (XXXVII).

The Kolbe Synthesis.[34]—This involves the electrolytic oxidation of a carboxylate ion under conditions of very high anodic potential. An active oxidizing agent of high potential such as persulfate ion forms the same products. Acetate ion yields carbon dioxide and ethane; propionate ion forms carbon dioxide, butane, ethane, ethylene, and ethyl propionate; other carboxylate ions yield similar products. The products from propionate ion may be accounted for by the process

$$C_2H_5CO_2^- \rightarrow C_2H_5CO_2 + e \qquad \text{(XLIII)}$$
$$C_2H_5CO_2 \rightarrow C_2H_5 + CO_2 \qquad \text{(XLIV)}$$
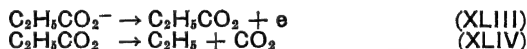
followed by known or reasonable reactions of the ethyl radical. These are reaction (XLII) for the butane, reaction (XXXVII) for the ethane and ethylene, and the process

$$C_2H_5 + C_2H_5CO_2 \rightarrow C_2H_5CO_2C_2H_5 \qquad \text{(XLV)}$$

for the ethyl propionate.

Radicals in the Decomposition of Diazotates and Related Reactions.[35]—When an aqueous solution of a sodium diazotate is stirred with benzene or one of its substitution products, a diphenyl derivative is formed[36]

$$[C_6H_5 - \bar{N} = \bar{N} - \bar{O}\,{}^!]^- + C_6H_6 \rightarrow C_6H_5 - C_6H_5 + N_2 + OH^- \quad \text{(XLVI)}$$

The reaction has entirely different properties from those which involve the attack of a carbonium ion or other electrophilic reagent on the benzene ring (page 309). The reaction with

[34] FICHTER *et al.*, *Helv. Chim. Acta*, **16**, 885 (1933); **18**, 704; 1276 (1935); **19**, 149 (1936).

[35] HEY and WATERS, *Chem. Rev.*, **21**, 169 (1937).

[36] GOMBERG and BACHMANN, *J. Am. Chem. Soc.*, **46**, 2339 (1924).

nitrobenzene is faster than that with toluene,[37] instead of slower, and produces *p*-nitrodiphenyl rather than the meta derivative. It seems, therefore, probable[37] that the intermediate is a phenyl radical rather than a carbonium ion. The same kind of evidence indicates that phenyl and substituted phenyl radicals may be formed from nitrosoacetanilides $C_6H_5N(NO)COCH_3$, from arylazotriphenylmethyls C_6H_5—N=N—$C(C_6H_5)_3$, and from diacylperoxides. When heated in solution all these substances abstract hydrogen from alcohols yielding aldehydes, or chlorine from carbon tetrachloride, or they form diphenyl derivatives substituted in the para position. Furthermore, and very characteristically, they attack tin, copper, mercury, and other metals forming water-soluble metallic salts.[38]

Semiquinones.[39]—As the stable filled shells of all atoms contain an even number of electrons, the usual stable organic molecule also contains an even number of electrons. The most familiar odd-electron carbon compound is triphenylmethyl, which is stabilized against the polymerization which is the common fate of such substances, by the distribution of the odd electron over a large volume (page 29). The substance is still a powerful reducing agent, however, and can be preserved only in the absence of oxygen. Recent investigation has shown that this need not be the case with all odd-electron substances and that relatively stable substances of this sort, to which the generic name of semiquinone has been given, may often be formed in oxidation or reduction reactions. The simplest case is that of the reduction .of tetramethylquinone in strongly alkaline solution (pH = 13).[40]

If a solution of the quinone (symbol T) is treated with a reducing agent, the reaction

$$C_6(CH_3)_4O_2 + 2H^+ + 2e \rightleftharpoons C_6(CH_3)_4(OH)_2 \qquad (XLVII)$$

requires two equivalents of reducing agent for each mole of hydroquinone (symbol R) produced. An inert electrode immersed in the solution develops a potential E, which is given by

[37] GRIEVE and HEY, *J. Chem. Soc.*, 1797 (1934).

[38] WATERS, *J. Chem. Soc.*, 113 (1937).

[39] MICHAELIS, *Chem. Rev.*, **16**, 242 (1935). MICHAELIS and SCHUBERT, *ibid.*, **22**, 437 (1938).

[40] MICHAELIS, SCHUBERT, REBER, KUCK, and GRANICK, *J. Am. Chem. Soc.*, **60**,.1678 (1938).

$$E = E^\circ + \frac{RT}{2F} \ln \frac{[\text{T}]}{[\text{R}]} \tag{3}$$

or

$$p = \frac{[\text{T}]}{[\text{R}]} = e^{2F(E-E^\circ)/RT} \tag{4}$$

for any constant pH, and a plot of values of E against titer of reducing agent represents a potentiometric titration curve. If, in addition, a semiquinone S is formed by the addition of one electron and exists in equilibrium with R and T

$$\text{R} + \text{T} \rightleftharpoons 2\text{S} \tag{XLVIII}$$

the equilibrium law applies in the form

$$\frac{[\text{S}]^2}{[\text{R}][\text{T}]} = K_1 \tag{5}$$

Like triphenylmethyl the odd-electron semiquinone must tend to dimerize according to the law

$$2\text{S} \rightleftharpoons \text{D} \tag{XLIX}$$

hence,

$$\frac{[\text{D}]}{[\text{R}][\text{T}]} = K_2 \tag{6}$$

If a represents the initial concentration of quinone and ax the number of equivalents per liter of reducing agent added, the equations

$$a = [\text{R}] + [\text{S}] + [\text{T}] + 2[\text{D}] \tag{7}$$
$$ax = [\text{S}] + 2[\text{D}] + 2[\text{R}] \tag{8}$$

are required by the stoichiometry. Equations (4) to (8) may be reduced to a single relationship between p and x, which is in effect the equation of the titration curve

$$2 + K_1^{\frac{1}{2}}p^{\frac{1}{2}} + (4K_2ax - 4K_2a - 2)p - K_1^{\frac{1}{2}}p^{\frac{3}{2}} + (p - 1)\sqrt{(2 + K_1^{\frac{1}{2}}p^{\frac{1}{2}})^2 + 8K_2pax} = 0 \tag{9}$$

In spite of its complicated form this equation has a number of simple corollaries. In the first place $p = 1$ when $x = 1$. Since the complete reduction of quinone to hydroquinone corresponds to $x = 2$, and since $E = E^\circ$ when $p = 1$, this implies that the

potential at the halfway point in the titration always gives the value of the molar potential $E°$. In the second place the quantity a appears in the equation only in the product K_2a. If, therefore, a series of titrations made with different values of a yield identical titration curves, the quantity K_2 must be so small that all the terms involving K_2a may be neglected. In this experimentally recognizable case the extent of dimerization is, therefore, negligible.

Finally, the slope $dE/dx = (RT/2F)d \ln p/dx$ at the mid-point of the titration curve is given by

$$\frac{dE}{dx} = \frac{RT}{F} \frac{K_2a}{\frac{1}{2}K_1^{1/2} + 1 - \sqrt{1 + K_1^{1/2} + \frac{1}{4}K_1 + 2K_2a}} \quad (10)$$

If the mid-point slope is determined for two different values of the concentration a, values of K_1 and K_2 may be determined from equation (10) by graphical methods. The equation takes simple forms in the limiting cases of negligible and of almost complete dimerization. In the first case ($K_2 \ll K_1$) it reduces to

$$\frac{dE}{dx} = -\frac{RT}{F}\left(1 + \frac{1}{2}\sqrt{K_1}\right) \quad (11)$$

from which K_1 is easily determined; in the second ($K_2 \gg K_1$) it reduces to

$$\frac{dE}{dx} = -\frac{RT}{F}\sqrt{\frac{1}{2}K_2a} \quad (12)$$

which gives the value of K_2 immediately.

The results of this analysis are entirely unambiguous, since they depend only on thermodynamic relationships and the easily attainable condition that activity coefficients are constant. If semiquinone or its dimer is formed in appreciable amounts, the whole form of the titration curve differs in an unmistakable way from that observed when only quinone and hydroquinone are present; whereas the effect of dilution on the shape of the curve offers a reliable criterion of the presence of the dimer. The analysis is supported in a number of cases by colorimetric evidence based upon the intense colors that many semiquinones and dimers possess and by magnetic evidence.[41] With very rare

[41] MICHAELIS, BOEKER, and REBER, *J. Am. Chem. Soc.*, **60**, 202 (1938).

exceptions, compounds of the lighter elements containing an even number of electrons are diamagnetic, and odd-electron compounds are paramagnetic. The property of paramagnetism offers, therefore, a criterion for the presence of odd-electron substances and even a method for the determination of their concentration.

In general quinone, hydroquinone, semiquinone, and dimer are acids and bases; consequently, the molar potential $E°$ and the constants K_1 and K_2 are functions of the pH of the solution. Usually the semiquinone is formed in appreciable concentrations only in a restricted range of acidities. Thus the reduction of tetramethylbenzoquinone (duroquinone) at a pH of 13 gives unmistakable evidence of the presence of a semiquinone and of the absence of a dimer. The value of K_1 is of the order of unity, and the mid-point slope is, therefore, 50 per cent greater than would be the case in the absence of the semiquinone. In less alkaline solutions the concentration of semiquinone becomes negligible.

The reasons for such a dependence on acidity are qualitatively intelligible.[42] The stoichiometric concentration of hydroquinone that enters into equations (4), (5), and (6) is the sum of the concentrations of the substances H_2Q, HQ^-, and $Q^=$, which are related to each other and the oxonium-ion concentration by protolytic equilibrium relationships. In the same way the stoichiometric concentration of semiquinone is the sum of the concentrations of HQ and Q^-. Because of the special stability of symmetrical resonance systems, systems H_2Q, $Q^=$, Q^-, and Q are particularly favored. A region of pH in which the semiquinone exists chiefly as Q^- and the hydroquinone is present chiefly as HQ^- will, therefore, be the optimum one for the formation of semiquinone, and an increase or a decrease in pH will decrease its concentration.

Unsubstituted p-benzoquinone cannot be studied at high alkalinities, because of the rapid decomposition of the quinone; in neutral or acid solutions no appreciable amounts of semiquinone or dimer are present. The familiar substance quinhydrone is stable in the solid state only; its diamagnetism shows it to be a dimer. Its low solubility and intense color are frequent prop-

[42] SCHWARZENBACH and MICHAELIS, *J. Am. Chem. Soc.*, **60**, 1667 (1938).

erties of such dimers.   Phenanthraquinone-3-sulfonic acid forms both semiquinone and dimer in strongly alkaline solution, dimer only in acid ones.[41]

In addition to a considerable number of quinones[43] the following types of substances form odd-electron compounds on reduction: quinoneimines and diimines related to (H),[42] phenazines derived from (I), γ,γ'-dipyridyls (J), indigo and its derivatives, and other heterocycles.

H₃C - N̄ - CH₂

(H)   (I)   (J)

A substance of similar properties is also formed in the oxidation of benzoin, $C_6H_5COCHOHC_6H_5$, to benzil, $C_6H_5COCOC_6H_5$.[44]

The Mechanism of Oxidation-reduction Reactions.—The purely thermodynamic demonstration of the existence of semi-quinones has no direct bearing on the problem of the possible appearance of these substances as intermediates in the inter-conversion of hydroquinone and quinone, although it is presumptive evidence of importance.   Actually, oxidation-reduction or redox reactions are known to go by a variety of mechanisms. The direct transfer of a hydride ion from one molecule or ion to another constitutes an oxidation of the former by the latter and represents the probable mechanism of the Cannizaro reaction (page 351).   The reactions of atmospheric oxygen with organic compounds apparently find their easiest path that of a

[43] GEAKE and LEMON, *Trans. Faraday Soc.*, **34**, 1409 (1938).
[44] MICHAELIS and FETCHER, *J. Am. Chem. Soc.*, **59**, 1246 (1937).

radical chain in most cases (page 372).   Many of the redox reactions of inorganic chemistry depend upon the transfer of an oxygen atom.   Thus the oxidation of arsenite by iodine possesses kinetics consistent with the mechanism[45]

$$I_2 + 2H_2O \rightleftharpoons HIO + I^- + OH_3^+ \tag{L}$$
$$HIO + H_3AsO_3 \rightarrow HI + H_3AsO_4 \tag{LI}$$
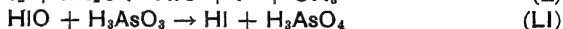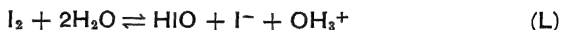
with the oxygen transfer (LI) rate determining.

The simplest process in appearance is the direct transfer of an electron from reductant to oxidant.   When the transfer is to or from an electrode in an electrochemical process, reactions that require merely the loss or gain of an electron are usually so rapid that the rate-determining process becomes the diffusion or electrolytic migration of the reactants to the electrode or of the reaction products away from it.   This is just as true of reactions involving stable complex ions such as

$$Fe(CN)_6^{\equiv} + e \rightleftharpoons Fe(CN)_6^{\equiv} \tag{LII}$$
$$MnO_4^- + e \rightleftharpoons MnO_4^{\equiv} \tag{LIII}$$
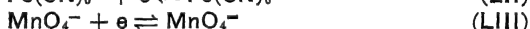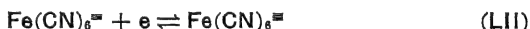
as it is of simple hydrated ions, $e.g.$,

$$Fe(H_2O)_6^{+++} + e \rightleftharpoons Fe(H_2O)_6^{++} \tag{LIV}$$

According to all the available evidence, therefore, the activation energy necessary for an electron transfer is extremely small.   By contrast, reactions involving changes in covalent linkages such as

$$CrO_4^- + 8H^+ + 3e \rightarrow Cr^{+++} + 4H_2O \tag{LV}$$
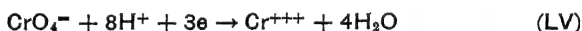
are likely to be sluggish and to require a considerable excess potential, called an $overvoltage$, over that theoretically necessary for the reaction before the rate reaches a detectable value.

Systems that are sluggish in their interaction with an electrode are also sluggish when brought in contact with other redox systems in solution.   Thus the reaction in dilute sulfuric acid solution

$$Ce^{++++} + \tfrac{3}{2}H_2O \rightleftharpoons Ce^{+++} + \tfrac{1}{4}O_2 + OH_3^+ \tag{LVI}$$
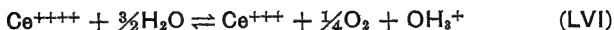
is accompanied by a free-energy decrease of 4000 calories and is, therefore, entirely possible in the thermodynamic sense.   Yet its rate is so low that ceric sulfate is indefinitely stable in this medium.   The ceric-cerous system is a mobile one in contact

[45] BRAY, $Z.$ $physik.$ $Chem.$, **54**, 463 (1906).

with an electrode, but the oxygen reaction requires a high overvoltage.

The Shaffer Hypothesis.[46]—Two electrochemically mobile systems may nevertheless fail to react, the limiting conditions being apparently the necessity of a three-body collision. Thus the reaction

$$2Ce^{++++} + Tl^+ \rightarrow 2Ce^{+++} + Tl^{+++} \qquad \text{(LVII)}$$
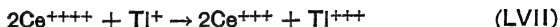
fails to take place measurably at 100°c, in spite of the fact that both the ceric-cerous and the thallic-thallous system are mobile electrochemically. If Tl^+ must lose two electrons at once or none, reaction (LVII) can occur only if a Tl^+ comes in contact simultaneously with two Ce^{++++} ions, a very improbable situation. Any kind of substance that can accept either one or two electrons should serve as a carrier; in fact, manganese compounds are effective catalysts for reaction (LVII). Since manganese compounds derived from the ions Mn^{++}, Mn^{+++}, and Mn^{++++} are known, the catalysis may be attributed to the sequence of reactions

$$Ce^{++++} + Mn^{++} \rightarrow Ce^{+++} + Mn^{+++} \qquad \text{(LVIII)}$$
$$Ce^{++++} + Mn^{+++} \rightarrow Ce^{+++} + Mn^{++++} \qquad \text{(LIX)}$$
$$Mn^{++++} + Tl^+ \rightarrow Mn^{++} + Tl^{+++} \qquad \text{(LX)}$$
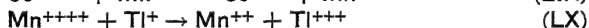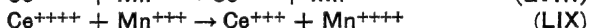
All these take place by two-body collisions only.

Similarly, the reaction

$$2Ti^{+++} + I_3^- \rightarrow 2Ti^{++++} + 3I^- \qquad \text{(LXI)}$$

is markedly catalyzed by naphthoquinones, anthraquinones, indigotin, pyocyanines, and other organic substances that can be reduced one electron at a time through a semiquinone stage.

Mobile Redox Systems in Organic Chemistry.—Like the inorganic systems, organic redox systems requiring only an electron transfer are mobile. Various triphenylcarbonium ions in acetic acid solution are rapidly and quantitatively reduced by chromous or titanous ion, and mixtures of radical and carbonium ion come to equilibrium with an inert electrode in such a way that the oxidation potential can be measured.[47] The reduction of iodine by triphenylmethyl is practically instantaneous, and triphenyl-

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[46] SHAFFER, *J. Am. Chem. Soc.*, **55**, 2169 (1933); *J. Phys. Chem.*, **40**, 1021 (1936).

[47] CONANT and CHOW, *J. Am. Chem. Soc.*, **55**, 3752 (1933).

methide ion is also an extremely active reducing agent. The fact that the rate-determining step in the reaction of iodine with hexaphenylethane is the dissociation into the radical (page 371) may be pertinent to the mechanism of many oxidation-reduction reactions.

Systems involving quinones, hydroquinones, and semiquinones are sufficiently mobile to permit the measurement of reversible oxidation potentials, although the reaction on an electrode surface is not immeasurably fast like the ferric-ferrous one. Hydroquinone is, of course, in mobile protolytic equilibrium with the ion $C_6H_4O_2^=$, which differs from quinone only by two electrons, and the mobility of the system may well be due to the latter fact. Other systems that have a comparable mobility are obtained by oxidation of indophenol and indamines or by reduction from indigo and its sulfonic acids; others are the azo-hydrazo benzene, the nitrosobenzene-hydroxylamine, and the hemoglobin-methemoglobin system.[48]

Redox Potentials of Quinone-hydroquinone Systems.—Table I contains the redox potentials of a variety of quinone-hydroquinone systems. These are the molar potentials for the reaction

$$Q + 2H^+ + 2e \rightleftharpoons H_2Q \qquad \text{(LXII)}$$

i.e., the potentials at unit activity of all reactants measured in alcoholic HCl solution. The effect of a substituent on the potential varies somewhat with the medium.

Effective Potentials.—In many cases an oxidation or a reduction is sluggish but can nevertheless be driven by the use of an oxidizing or reducing agent of sufficiently positive or negative potential. In effect this amounts to the same thing as an electrolytic oxidation under conditions of high overvoltage. If the rate of the reaction depends, as it sometimes does, upon the potential of the oxidizing or reducing agent alone and not on its specific nature, a useful "effective potential" may be measured. This is the potential at which the rate of oxidation or of reduction of the sluggishly reacting substance becomes perceptible.

The simplest method of measuring an effective potential is to test the reaction of the substance to be measured with a series of dyestuffs that themselves constitute mobile redox systems and

[48] These systems are reviewed by Clark, *Chem. Rev.*, **2**, 127 (1925).

by their color change indicate whether or not reaction has occurred. Because of the interest in such measurements in biological systems, many oxidation indicators of this sort have been carefully studied and their potentials under various conditions of acidity determined.[48] Any other method that determines whether or not the sluggishly reacting system reacts with

TABLE I.—MOLAR OXIDATION POTENTIALS OF QUINONE-HYDROQUINONE
SYSTEMS
(Alcoholic solution at 25°)[49]

Quinone	$E°$	Quinone	$E°$
p-Benzoquinone............	+0.711	Tetrachlor-p-benzoquinone.	+0.703
Methyl-p-benzoquinone.....	0.656	Brom-benzoquinone.......	0.735
p-Dimethyl-benzoquinone...	0.597	Ethyl-benzoquinone.......	0.658
Tetramethyl-benzoquinone..	0.466	Hydroxy-benzoquinone....	0.599
p-Methyl, i-propyl-benzo-quinone................	0.589	1,4-Naphthoquinone.......	0.484
Chlor-benzoquinone........	0.736	1,4-Naphthoquinone-	
2,3-Dichlor-benzoquinone...	0.711	2-sulfonate..............	0.553
2,5-Dichlor-benzoquinone...	0.734	2-Hydroxy-1,4-naphtho-	
2,6-Dichlor-benzoquinone...	0.748	quinone.................	0.357
Trichlor-benzoquinone.....	0.726	1,2-Naphthaquinone.......	0.580
		9,10-Anthraquinone.......	0.156

a mobile redox system of known potential may also be used for the determination of effective potentials. The effective potentials for the reduction of the following substances in 0.2M aqueous HCl were determined by methods of this sort:[50] $HSO_3C_6H_4N=NC_6H_4OH$, +0.42; C_6H_5—CO—CH=CH—COOH, +0.06; cis HOOC—CH=CH—COOH, −0.25; 2,4-dinitrobenzoic acid, +0.23; m-nitrobenzoic acid, +0.06.

An effective potential may also be measured by determining the potential that must be applied externally to an electrode in order that the substance may be oxidized or reduced at a perceptible rate. The otherwise difficult problem of obtaining an

[49] CONANT and FIESER, J. Am. Chem. Soc., 45, 2194 (1923); 46, 1858 (1924). LAMER and BAKER, ibid., 44, 1954 (1922). KVALNES, ibid., 56, 670 (1934). FIESER and FIESER, ibid., 56, 1565 (1934). FIESER and PETERS, ibid., 53, 793 (1931).
[50] CONANT, Chem. Rev., 3, 1 (1926).

electrode of reproducible properties may be solved by the use of Heyrovskii's dropping mercury electrode technique, in which the electrolytic process occurs on a constantly renewed surface of purified mercury. Some results on carbonyl compounds obtained by this method follow.[51] Acetone, acetylacetone, and cyclopentanone have potentials so negative that no perceptible reduction can be obtained. The values of aliphatic aldehydes are in the neighborhood of -1.9 volts, those for phenyl alkyl ketones, from -1.5 to -1.6; for benzophenone and benzaldehyde, -1.3; for benzalacetophenone and other unsaturated ketones and for pyruvic acid, -1.1 to -1.2; for p-benzoquinone, -0.1; for diacetyl, -0.93; for benzil -0.7. In phenyl derivatives the introduction of hydroxyl or of methoxyl makes the potential more negative.

The Addition of Electrons to Unsaturated Systems.—Given a sufficiently high-pressure source of electrons, which in practice usually means an alkali metal, many unsaturated substances add electrons directly. Thus benzophenone reacts either with one or with two atoms of sodium,[52] forming products that are electrolytes in liquid ammonia solution.[53] The reactions are

$$C_6H_5 - \underset{\underset{O}{\|}}{C} - C_6H_5 + Na \rightarrow \left[C_6H_5 - \underset{\underset{O}{|}}{\dot{C}} - C_6H_5 \right]^- + Na^+ \quad (LXIII)$$

$$\left[C_6H_5 - \underset{\underset{O}{|}}{\dot{C}} - C_6H_5 \right]^- + Na \rightarrow \left[C_6H_5 - \underset{\underset{O}{|}}{\ddot{C}} - C_6H_5 \right]^- + Na^+ \quad (LXIV)$$
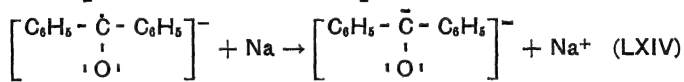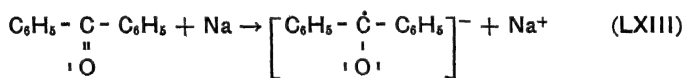
The radical produced in reaction (LXIII) is largely dimerized

$$2 \left[\underset{\underset{O}{|}}{\overset{\overset{C_6H_5}{|}}{C_6H_5 - C\cdot}} \right]^- \rightleftharpoons \left[\underset{\underset{O}{|}}{\overset{\overset{C_6H_5 \quad C_6H_5}{|}}{C_6H_5 - C\text{——}C - C_6H_5}} \right]^- \quad (LXV)$$
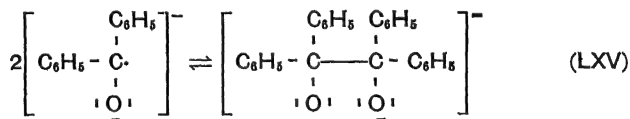
If an acid such as ammonium ion or water is added, the ions accept protons, e.g.,

[51] ADKINS and COX, J. Am. Chem. Soc., 60, 1151 (1938).
[52] SCHLENK and WEICHSEL, Ber., 44, 1182 (1911). SCHLENK and THAL, ibid., 46, 2840 (1913).
[53] KRAUS and BIEN, J. Am. Chem. Soc., 55, 3609 (1933).

$$\left[C_6H_5 - \overset{\_}{\underset{\underset{\bullet}{|}{O \bullet}}{C}} - C_6H_5 \right]^- + 2NH_4^+ \rightarrow C_6H_5 - \overset{\overset{H}{|}}{\underset{\underset{\bullet}{|}{O - H}}{C}} - C_6H_5 + 2NH_3 \qquad (LXVI)$$

$$\left[C_6H_5 - \overset{\overset{C_6H_5}{|}}{\underset{\underset{\bullet}{|}{O \bullet}}{C}} \overset{\overset{C_6H_5}{|}}{\underset{\underset{\bullet}{|}{O \bullet}}{C}} - C_6H_5 \right]^- + 2NH_4^+ \rightarrow C_6H_3 - \overset{\overset{C_6H_5}{|}}{\underset{\underset{\bullet}{|}{O - H}}{C}} \overset{\overset{C_6H_5}{|}}{\underset{\underset{\bullet}{|}{O - H}}{C}} - C_6H_5 + 2NH_3$$
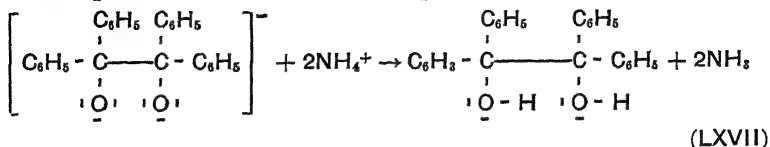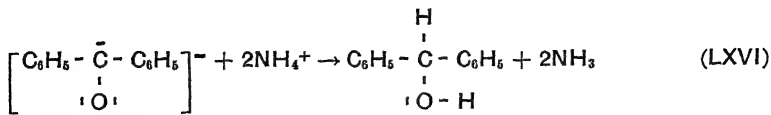
$$(LXVII)$$

and benzhydrol and benzpinacol are formed.

The same sequence of reactions might occur when the metal acts on the ketone in the presence of the acid, in which case reactions (LXVI) and (LXVII) would follow very rapidly on reactions (LXIII), (LXIV), and (LXV). This process offers a very satisfactory mechanism for the reduction of a carbonyl compound by sodium and alcohol, by zinc and hydrochloric acid, or by any similar system.[54] Since esters react with sodium metal in liquid ammonia solution in the same way that ketones do,[55] a similar mechanism may well be involved in the reduction of esters by sodium and alcohol. The fact that alcohol instead of ether is formed may be attributed to the loss of alkyloxy ion from an intermediate formed by reactions analogous to (LXIII) and (LXIV)

$$\left[R - \overset{\_}{\underset{\underset{\bullet}{|}{O \bullet}}{C}} - \overset{\_}{O} - R' \right]^- \rightarrow \left[R - \overset{\_}{\underset{\underset{\bullet}{\|}{O \bullet}}{C}} \right]^- + [\bullet \overset{\_}{O} - R']^- \qquad (LXVIII)$$
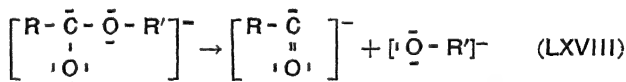
The product is the conjugate base of the aldehyde RCHO, the rapid further reduction of which yields the alcohol. The impossibility of reducing an acid by this method is due to the fact that the molecular acid prefers to accept an electron on its acid hydrogen

$$RCOOH + e \rightarrow RCOO^- + H\cdot \qquad (LXIX)$$
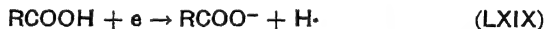
with the eventual formation of molecular hydrogen, whereas the negative charge on the carboxylate ion must greatly hinder the acceptance of an electron.

[54] WILLSTÄTTER, SEITZ, and BUMM, *Ber.*, **61**, 871 (1928).

[55] KHARASCH, STERNFELD, and MAYO, paper presented before the Division of Physical and Inorganic Chemistry of the American Chemical Society at the Milwaukee meeting, September, 1938.

Even olefins, provided that they contain conjugated systems, may accept electrons.[56] Thus stilbene adds two sodium atoms to form an ionic substance

$$C_6H_5 - CH = CH - C_6H_5 + 2Na\cdot \rightarrow [C_6H_5 - \bar{C}H - \bar{C}H - C_6H_5]^- + 2Na^+$$
(LXX)
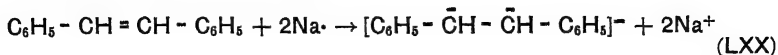
the reaction of which with acids yields diphenylethane, and styrene yields a product analogous to a pinacol

$$C_6H_5 - CH = CH_2 + Na\cdot \rightarrow [C_6H_5 - \bar{C}H - \dot{C}H_2]^- + Na^+ \qquad \text{(LXXI)}$$

$$2[C_6H_5 - \bar{C}H - \dot{C}H_2]^- \rightarrow [C_6H_5 - \bar{C}H - CH_2 - CH_2 - \bar{C}H - C_6H_5]^- \quad \text{(LXXII)}$$
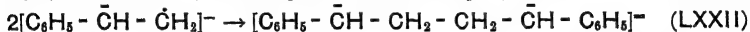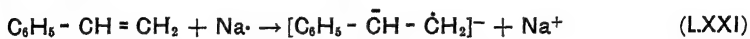
[56] Schlenk, Appenrodt, Michael, and Thal, *Ber.*, **47**, 473 (1914).

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